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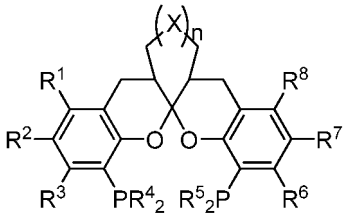
(54) COMPOUNDS OF CHIRAL AROMATIC SPIROKETAL DIPHOSPHINE LIGANDS, PREPARATION METHODS AND USES THEREOF

(57) Disclosed are aromatic spiroketal diphosphine ligands, preparation methods and uses thereof. The ligands have the structure of formula (I), in which R1, R2, R3, R4, R5, R6, R7, R8, X and n are defined as such described in the specification. The aromatic spiroketal diphosphine ligands are prepared from aromatic spiroketal compounds. Also disclosed are the preparation methods of aromatic spiroketal compounds. The preparation methods are simple and can produce racemic or chiral aromatic spiroketal diphosphine ligands. The ligands can be used as catalysts of asymmetrical catalytic reactions having economical practicability and industry application prospect.



(I)

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Description

Technical field

[0001] The present invention relates to the filed of organic chemistry, specially, to a chiral aromatic spiroketal bisphosphine ligand, preparation method and use thereof.

Background art

[0002] Catalytic asymmetric synthesis is the research hotspot in the field of organic synthesis chemistry (Ohkuma, T.; Kitamura, M.; Noyori, R. 1999, Catalytic asymmetric synthesis. 2nd Ed.). Design and development of excellent chiral ligands and catalyst systems play a central role in asymmetric catalytic synthesis. Because chiral spirane structures (such as chiral aromatic spiroketals) have good rigid structure and formed transition metal complexes have advantages such as high stereoselectivity and chemical selectivity, etc. in asymmetric catalytic reactions, the studies on such ligands have received much attention from organic chemistry researcher (Acc. Chem. Res. 2008, 41, 581; Chem. Asian J. 2009, 4, 32.). In recent years, aromatic spiroketal ligands gradually got attention by people. For example, the complex formed from SPANPhos having benzodihydopyran backbone and metal rhodium showed good catalytic performance in the carbonylation of methanol for preparing formic acid (Angew. Chem. Int. Ed. 2003, 42, 1284; Angew. Chem. Int. Ed. 2005, 44, 4385). Another bisoxazoline ligand SPANBox having chiral aromatic spiroketal backbone has successfully been applied in asymmetric electrophilic hydroxylation of β-dicarbonyl compound catalyzed by Zn(II) (Chem. Sci. 2011, 2, 1141). However, the synthesis of benzodihydopyran backbone is relatively complicated and the yield is low. Moreover, it is difficult to adjust the backbone. Only racemic backbone can be obtained and further resolution is necessary to obtain optical pure backbone, which is not economic or environmentally friendly.

[0003] Chiral aromatic spiroketal is an important structure unit of natural products, bioactive compounds and chiral ligands. Reported methods includes spiroketalization of bisphenol hydroxy-ketone (or analogues) under the catalysis of acids (Tetrahedron Lett. 1998, 39, 5429; J. Chem. Soc., Perkin Trans. 1 2000, 2681; Org. Lett. 2006, 8, 4875; Tetrahedron 2006, 62, 5883; Synthesis 2008, 22, 3605), etherification of benzofuran under halogen (Angew. Chem. Int. Ed. 2001, 40, 4709), intramolecular addition reaction of hydroxy unsaturated bond catalyzed by transition metal (Synlett 2008, 940.), Mitsunobu reaction (Angew. Chem. Int. Ed. 2001, 40, 4713), aromatic Pumerer reaction (Angew. Chem. Int. Ed. 2007, 46, 7458), cycloaddition reaction (J. Org. Chem. 1997, 62, 1058; Org. Lett. 2006, 8, 2365; Tetrahedron Lett. 2006, 47, 3349) and so on. However, these methods are limited to synthesize racemic aromatic spiroketal products. Generally, the resolution of racemic aromatic spiroketal products is necessary to obtain optical pure chiral aromatic spiroketal compounds. The process is complicated and not economic or environmentally friendly.

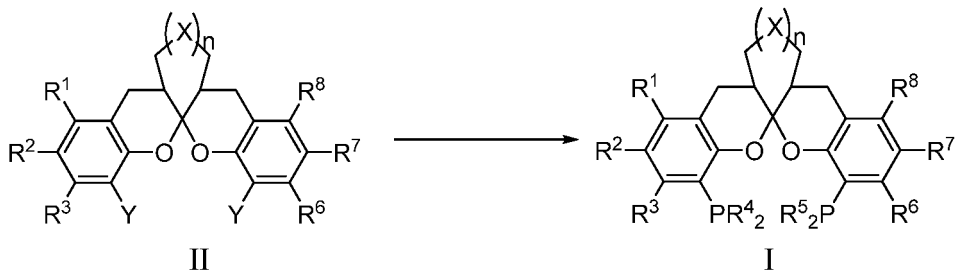
[0004] It is necessary in the art to develop a novel aromatic spiroketal compound and a preparation method for chiral ligand, thereby obtaining racemates or compounds having optocal activity (opitcal pure) through simple reaction to avoid resolution.

Summary of the invention

[0005] One object of the present invention is to provide a chiral aromatic spiroketal bisphosphine ligand, synthesis method and use thereof.

[0006] Another object of the present invention is to provide a preparation method for chiral aromatic spiroketal compounds.

[0007] In the first aspect of the present invention, a preparation method for a compound of formula I is provided, comprising the step of synthetizing the compound of formula I from a compound of formula II,

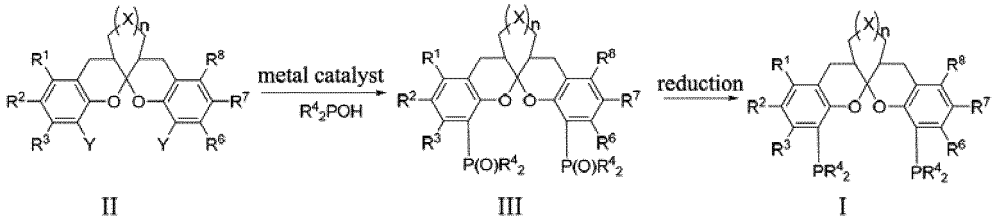


wherein R^1, R^2, R^3, R^6, R^7 and R^8 are independently selected from a hydrogen, a halogen, substituted or unsubstituted following groups: a C_1-C_{10} alkyl, a C_1-C_4 alkoxyl, a C_3-C_{30} cycloalkyl or an aryl;

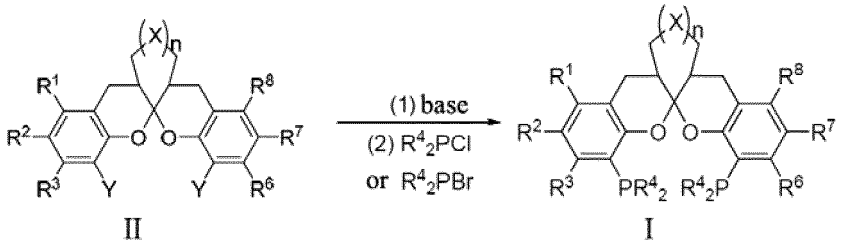
R^4 and R^5 are independently selected from substituted or unsubstituted following groups: a C_3-C_{10} cycloalkyl, a C_1-C_{10} alkyl, 2-furyl, or an aryl;
X is selected from CH_2, NH, NCH_3, O or S; n = 0 - 4;
wherein the substitution refers to be substituted by the following substituents: a halogen, a C_{1-6} alkyl, a C_{1-6} haloalkyl, or a C_{1-6} alkoxyl;
Y is F, Cl, Br or I.

[0008] In another preferred embodiment, R^5 are identical with R^4, and the method includes the steps:

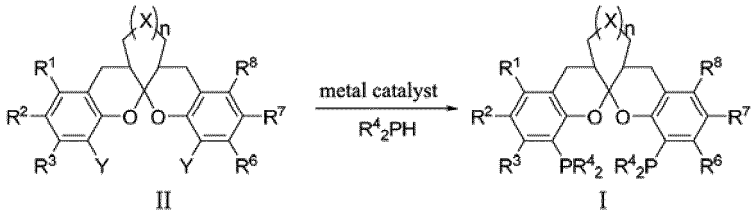
(a1) a compound of formula II reacts with $R^4{}_2POH$ in an organic solvent under the action of a metal catalyst to obtain a compound of formula III;
(b1) the compound of formula III is reduced to obtain the ligand,



or includes the step:
(a2) in an organic solvent and under the action of a base, Y group is removed from the compound of formula II and then the compound of formula II reacts with $R^4{}_2PCl$ or $R^4{}_2PBr$ to obtain the ligand,



or includes the step:
(a3) the compound of formula II reacts with $R^4{}_2PH$ in an organic solvent and under the action of a metal catalyst to obtain the ligand;



wherein Y is Cl, Br or I; R^1, R^2, R^3, R^4, R^6, R^7, R^8, X and n are defined as above.

[0009] In another preferred embodiment, in step (a2), the mole ratio of the base to the compound of formula II is 2: 1 - 10: 1; and the mole ratio of $R^4{}_2PCl$ or $R^4{}_2PBr$ to the compound of formula II is 2: 1 - 10: 1.

[0010] In another preferred embodiment, said metal catalyst is at least one selected from $Pd(OAc)_2$, $PdCl_2$, $Pd_2(dba)_3$, $Pd(dba)_2$, $[Pd(C_3H_5)Cl]_2$, $Pd(PPh_3)_4$, $Pd(PPh_3)_2Cl_2$, $Pd(CH_3CN)Cl_2$, dpppNiCl$_2$, $Ni(PPh_3)_2Cl_2$, CuI, or a combination thereof

[0011] In another preferred embodiment, in step (a3), the mole ratio of the metal catalyst to the compound of formula II is 0.001 - 0.5: 1; the mole ratio of $R^4{}_2PH$ to the compound of formula II is 2 - 10: 1.

[0012] In another preferred embodiment, in step (a1), the mole ratio of the metal catalyst to the compound of formula II is 0.001 - 0.5: 1; the mole ratio of $R^4{}_2POH$ to the compound of formula II is 2 - 10: 1.

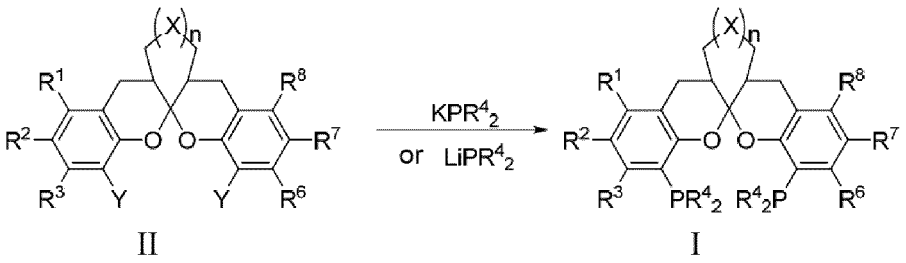
[0013] In another preferred embodiment, in step (b1), the reducing agent is selected from $HSiCl_3$, $(Me_2SiH)_2O$, $LiAlH_4$,

$(EtO)_3SiH$, or a combination thereof.

[0014] In another preferred embodiment, said organic solvent is at least one of benzene, toluene, xylene, dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane, diethyl ether, tetrahydrofuran, methanol, ethanol, *N,N*-dimethyl formamide or dimethyl sulfoxide, or a mixture thereof.

[0015] In another preferred embodiment, said base is selected from n-butyl lithium, tert-butyl lithium, cyclohexyl lithium, methyl lithium, isopropyl lithium, lithium bis(trimethylsilyl)amide, sodium bis(trimethylsilyl)amide, potassium bis(trimethylsilyl)amide, ethyl magnesium chloride, ethyl magnesium bromide, phenyl magnesium chloride, phenyl magnesium bromide.

[0016] In another preferred embodiment, R^5 is identical with R^4, and the method comprises the steps:



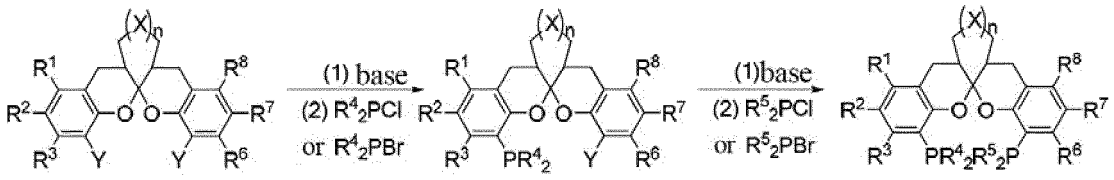
II I

the compound of formula II reacts with KPR^4_2 or $LiPR^4_2$ in an organic solvent to form the ligand, wherein Y is F; R^1, R^2, R^3, R^4, R^6, R^7, R^8, X and n are defined as above.

[0017] In another preferred embodiment, said organic solvent is at least one of benzene, toluene, xylene, dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane, diethyl ether, tetrahydrofuran, methanol, ethanol, *N,N*-dimethyl formamide or dimethyl sulfoxide, or a mixture thereof.

[0018] In another preferred embodiment, the mole ratio of KPR^4_2 or $LiPR^4_2$ to the compound of formula II is 2:1-10:1.

[0019] In another preferred embodiment, the method comprises the steps:



II IV I

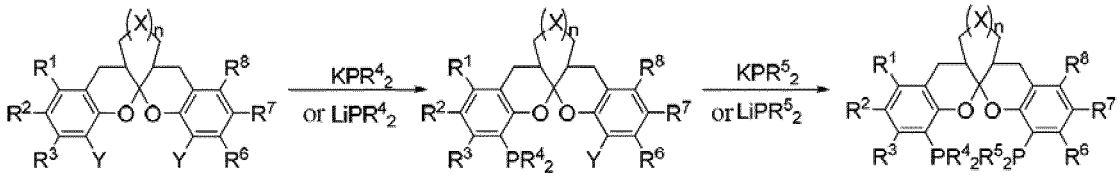
(i1) in an organic solvent, the compound of formula IIreacts with a base and then reacts with R^4_2PCl or R^4_2PBr to form a compound of formula IV;

(ii1) the compound of formula IV reacts with a base and then reacts with R^5_2PCl or R^5_2PBr to form the ligand,

wherein Y is Cl, Br or I;

R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, X and n are defined as above, and $R^4 \neq R^5$;

or comprises the steps: (i2) in an organic solvent, the compound of formula II reacts with KPR^4_2 or $LiPR^4_2$ to form the compound of formula IV;



II IV I

(ii2) the compound of formula IV reacts with KPR^5_2 or $LiPR^5_2$ to form the ligand,

wherein Y is F; R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, X and n are defined as above, and $R^4 \neq R^5$.

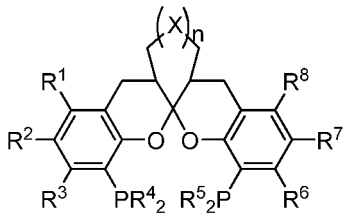
[0020] In another preferred embodiment, in step (i1), the mole ratio of the base to the compound of formula II is 1: 1 - 1.2: 1; and the mole ratio of $R^4{}_2PCl$ or $R^4{}_2PBr$ to the compound of formula II is 1: 1 - 1.2: 1; and/or
in step (ii1), the mole ratio of the base to the compound of formula IV is 1: 1 - 1.2: 1; and the mole ratio of $R^5{}_2PCl$ or $R^5{}_2PBr$ to the compound of formula IV is 1: 1 - 1.2: 1.

[0021] In another preferred embodiment, in step (i2), the mole ratio of $KPR^4{}_2$ or $LiPR^4{}_2$ to the compound of formula II is 1: 1 - 1.2: 1; and/or
in step (ii2), the mole ratio of $KPR^5{}_2$ or $LiPR^5{}_2$ to the compound of formula IV is 1: 1 - 1.2: 1.

[0022] In another preferred embodiment, said organic solvent is one of benzene, toluene, xylene, dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane, diethyl ether, tetrahydrofuran, methanol, ethanol, *N,N*-dimethyl formamide or dimethyl sulfoxide, or a mixture thereof.

[0023] In another preferred embodiment, said base is selected from n-butyl lithium, tert-butyl lithium, cyclohexyl lithium, methyl lithium, isopropyl lithium, lithium bis(trimethylsilyl)amide, sodium bis(trimethylsilyl)amide, potassium bis(trimethylsilyl)amide, ethyl magnesium chloride, ethyl magnesium bromide, phenyl magnesium chloride, phenyl magnesium bromide.

[0024] In the second aspect of the present invention, a ligand is provided, having a structure as shown in general formula I:



(I)

wherein,

R^1, R^2, R^3, R^6, R^7 and R^8 are independently selected from a hydrogen, a halogen, substituted or unsubstituted following groups: a C_1-C_{10} alkyl, a C_1-C_4 alkoxyl, a C_3-C_{30} cycloalkyl or an aryl;
R^4 and R^5 are independently selected from substituted or unsubstituted following groups: a C_3-C_{10} cycloalkyl, a C_1-C_{10} alkyl, 2-furyl, or an aryl; X is selected from CH_2, NH, NCH_3, O or S; n=0 - 4;
wherein the substitution refers to be substituted by the following substituents: a halogen, a C_1-$_6$ alkyl, a C_1-$_6$ haloalkyl, or a C_1-$_6$ alkoxyl,
"aryl" includes but not limited to phenyl, phenylene, naphthyl, naphthalene, pyrenyl, anthryl, phenanthryl.

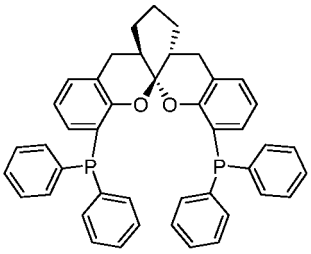
[0025] In another preferred embodiment, the ligand is prepared according to the method of the first aspect.

[0026] In another preferred embodiment, when all of R^1, R^2, R^3, R^6, R^7 and R^8 are hydrogen, X is CH_2 and n=1, not both of R^4 and R^5 are phenyl.

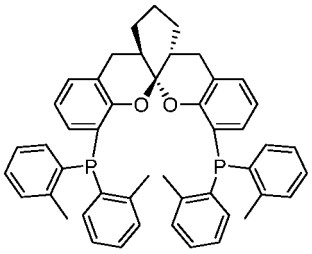
[0027] In another preferred embodiment, not both of R^4 and R^5 are phenyl.

[0028] In another preferred embodiment, R^1, R^2, R^3, R^6, R^7 and R^8 are independently selected from a hydrogen, a C_1-C_6 alkyl, a C_1-C_4 alkoxyl, a C_3-C_{10} cycloalkyl, a phenyl or a halogen;
R^4, R^5 are independently selected from a phenyl or a substituted phenyl, a C_3-C_6 cycloalkyl or a C_2-C_6 alkyl, and the substitution is mon-substituted, di-substituted or tri-substituted by the following substituents: a halogen, a C_1-$_6$ alkyl, a C_1-$_6$ haloalkyl, or a C_1-$_6$ alkoxyl;
X is selected from CH_2, O, NCH_3 or S. Preferably, when all of R^1, R^2, R^3, R^6, R^7 and R^8 are hydrogen, X is CH_2 and n=1, not both of R^4 and R^5 are phenyl. More preferably, not both of R^4 and R^5 are phenyl.

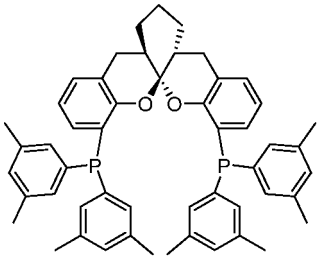
[0029] In another preferred embodiment, the ligand is any one selected from compounds of formulae 6a~6w, or enantiomers, racemates or diastereoisomers of the compounds of formulae 6a~6w:



6a



6b



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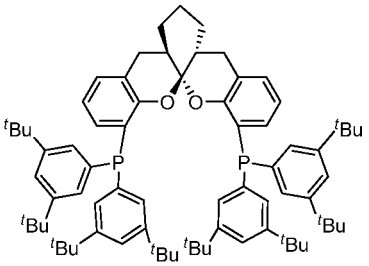
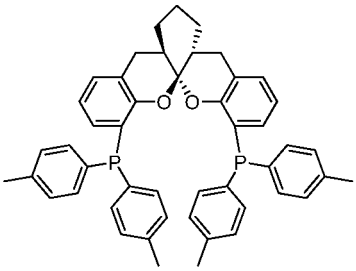


6d



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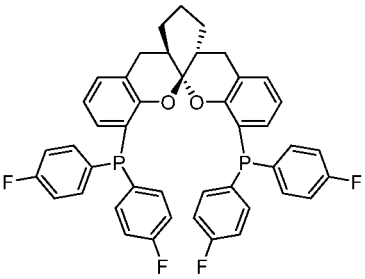

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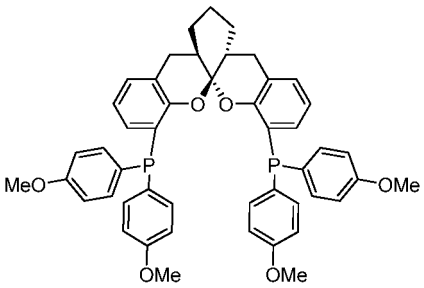
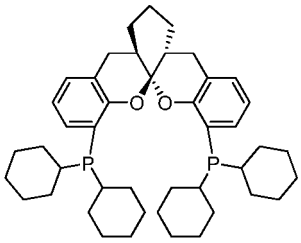
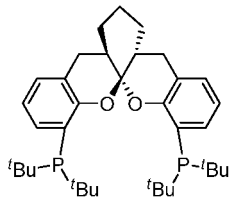


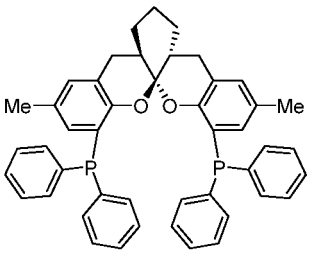
6g



6h



6i



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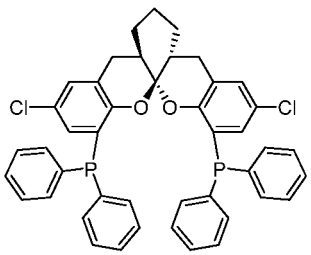
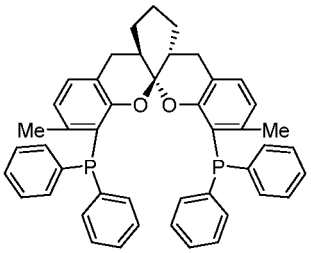
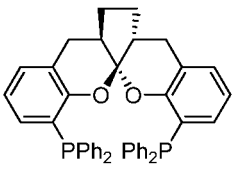


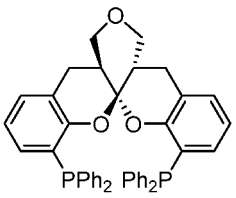
6k



6l



6m



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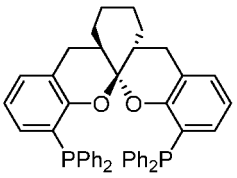

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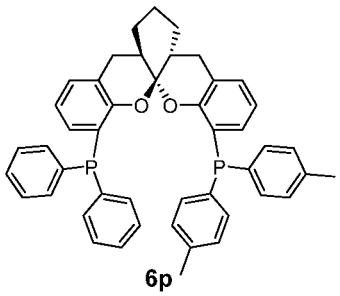
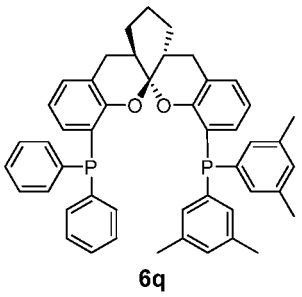
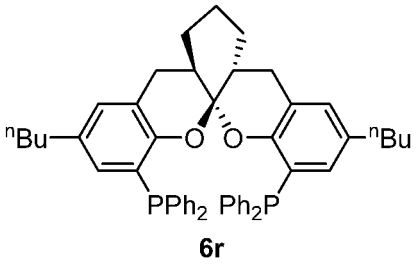
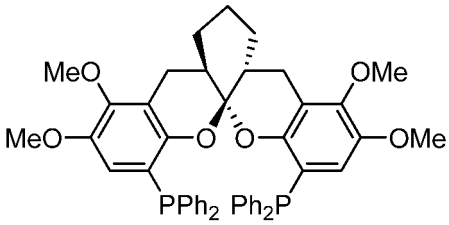
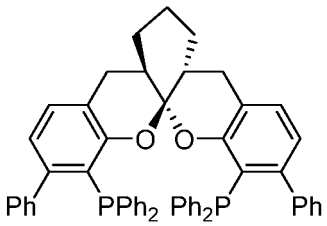
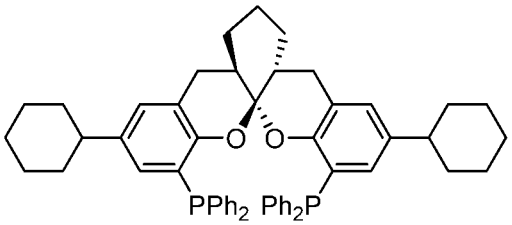


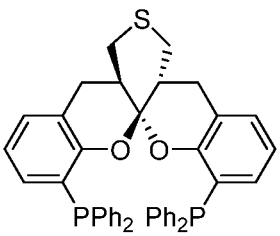


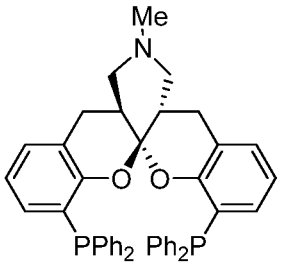










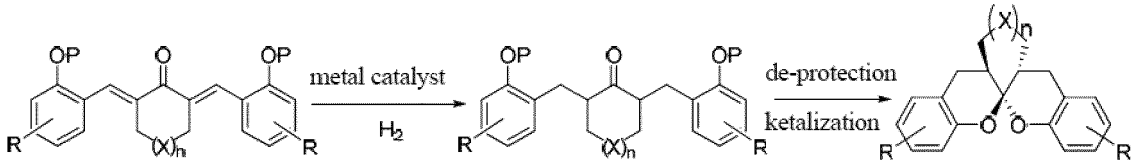


[0030] In the third aspect of the present invention, a use of the ligand of the second aspect is provided, for a catalyst or for synthesizing a catalyst.

[0031] In another preferred embodiment, the complex formed from the ligand and a metal is used as the catalyst.

[0032] In another preferred embodiment, the catalyst is a catalyst used for asymmetric catalytic reaction.

[0033] In the fourth aspect of the present invention, a preparation method for chiral aromatic spiroketal compounds is provided, comprising the following steps:



3-P 4-P V

(a) under hydrogen atmosphere, a compound of formula **3-P** as a substrate is subjected to catalytic hydrogenation in an organic solvent by using a metal complex as a catalyst to obtain a hydrogenated product, a compound of formula **4-P;**

(b) protecting groups are removed from the compound of formula **4-P,** and then the compound is subjected to ketalization to obtain a chiral aromatic spiroketal compound, wherein the chiral aromatic spiroketal compound is a compound of general formula V or an enantiomer, racemate or diastereoisomer thereof,

wherein, X is selected from CH_2, NH, NCH_3, O or S; n= 0 - 4; R on the left is one or more of R^{11}, R^{12}, R^{13} and R^{14}, R on the right is one or more of R^{15}, R^{16}, R^{17} and R^{18}, and R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17} and R^{18} are independently selected from a hydrogen, a C_1-C_{10} alkyl, a C_1-C_4 alkoxyl, a C_3-C_{30} cycloalkyl, a halogen or an aryl;

P is a methyl, a benzyl, a p-methoxy benzyl, a tert-butyl, a tert-butyldimethylsilyl, a tert-butyldiphenylsilyl, an allyl, a methoxymethyl, a methylthiomethyl, a methoxyethoxymethyl, a benzyloxymethyl, a tetrahydro 2-pyranyl or ester group.

[0034] In another preferred embodiment, the mole ratio of the compound of formula **3-P** to the metal complex catalyst is 10000: 1 - 10: 1.

[0035] In another preferred embodiment, the metal complex is a complex of metal rhodium, ruthenium, palladium or iridium.

[0036] In another preferred embodiment, the metal complex is a complex of phosphine-nitrogen ligand and iridium.

[0037] In another preferred embodiment, the catalytic hydrogenation reaction is carried out under 1-100 normal atmospheric pressure of hydrogen at -78 - 80 °C for 1-48 hrs.

[0038] In another preferred embodiment, said organic solvent is at least one of benzene, toluene, xylene, dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane, diethyl ether, tetrahydrofuran, methanol, ethanol, *N,N*-dimethyl formamide or dimethyl sulfoxide.

[0039] In another preferred embodiment, separation and purification can be carried out during the process from 4-P to V or from 3-P to 4-P to V. Alternatively, the reaction can be finished in one-pot without separation.

[0040] It should be understood that, within the scope of the present invention, the technical features specifically described above and below (such as the Examples) can be combined with each other, thereby constituting a new or preferred technical solution which needs not be described one by one.

SPECIFIC MODE FOR CARRYING OUT THE INVENTION

[0041] Upon extensive and in-depth research, chiral or racemic aromatic spiroketal bisphosphine ligands are prepared by the inventors of the present application using a simple reaction, so as to avoid resolution. Moreover, the ligand can be used as a catalyst in asymmetric catalytic reaction and has economic utility and industrial application prospect.

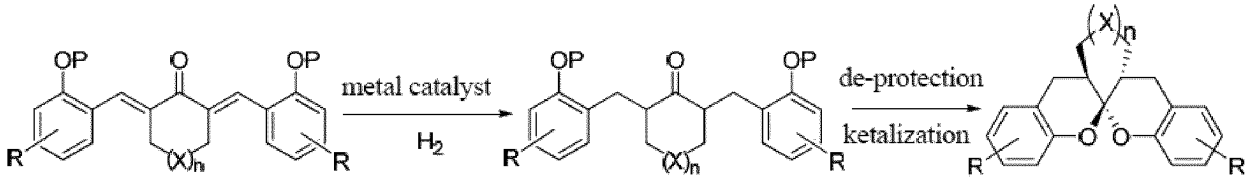
Term

[0042] The term "alkyl" refers to a saturated linear or branched chain-hydrocarbon moiety, such as $-CH_3$ or $-CH(CH_3)_2$. The term "alkoxy" refers to a group generated from binding an alkyl and oxygen atom, such as $-OCH_3$, $-OCH_2CH_3$. The term "cycloalkyl" refers to a saturated cyclic hydrocarbon moiety, such as cyclohexyl. The term "aryl" means a hydrocarbon moiety containing one or more aromatic rings, including but not limited to phenyl, phenylene, naphthyl, naphthalene, pyrenyl, anthryl, phenanthryl and benzyl.

[0043] Unless otherwise specified, the alkyl, alkoxy, cycloalkyl and aryl described herein include substituted or unsubstituted moieties. Feasible substituents on the alkyl, alkoxy, cycloalkyl and aryl may include, but are not limited to: a C_1-C_6 alkyl, a C_1-C_6 haloalkyl, a C_2-C_6 alkenyl, a C_2-C_6 alkynyl, a C_3-C_{10} cycloalkyl, a C_3-C_{10} cycloalkenyl, a C_1-C_6 alkoxy, an aryl, a hydroxy, a halogen, an amino.

Preparation method for aromatic spiroketal compounds

[0044] The preparation method for aromatic spiroketal compounds according to the present invention comprises the following steps:



3-P **4-P** **V**

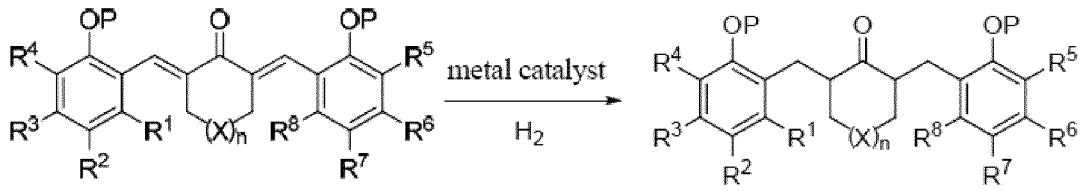
(a) under hydrogen atmosphere, a compound of formula **3-P** as a substrate is subjected to catalytic hydrogenation by using a metal complex as catalyst in an organic solvent to obtain hydrogenated product, a compound of formula **4-P;**

(b) the protecting groups are removed from the compound of formula **4-P,** and then the compound is subjected to ketalization to obtain a chiral aromatic spiroketal compound, wherein the chiral aromatic spiroketal compound is the compound having general formula V or an enantiomer, racemate or diastereoisomer thereof,

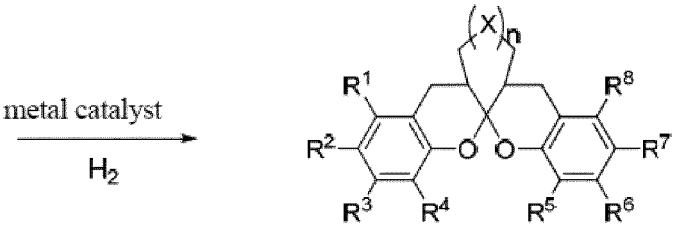
wherein X is selected from CH_2, NH, NCH_3, O or S; n= 0 - 4; R on the left is one or more of R^{11}, R^{12}, R^{13} and R^{14} R on

the right is one or more of R^{15}, R^{16}, R^{17} and R^{18}, and R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17} and R^{18} are independently selected from a hydrogen, a C_1-C_{10} alkyl, a C_1-C_4 alkoxyl, a C_3-C_{30} cycloalkyl, a halogen or an aryl;
P is a methyl, a benzyl, a p-methoxy benzyl, a tert-butyl, a tert-butyldimethylsilyl, a tert-butyldiphenylsilyl, an allyl, a methoxymethyl, a methylthiomethyl, a methoxyethoxymethyl, a benzyloxymethyl, a tetrahydro 2-pyranyl or ester group.

[0045] In another preferred embodiment, the preparation method for aromatic spiroketal compounds according to the present invention comprises the following steps:



3-P-1 **4-P-1**



I

(a') under hydrogen atmosphere, a compound of formula **3-P-1** as a substrate is subjected to catalytic hydrogenation in an organic solvent by using metal complex as catalyst to obtain hydrogenated product, a compound of formula **4-P-1;**

(b') the protecting groups are removed from the compound of formula **4-P-1,** and then the compound is subjected to ketalization to obtain a chiral aromatic spiroketal compound,

wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, X and n are defined as above.

[0046] In another preferred embodiment, the metal complex is chiral or non-chiral.

[0047] In another preferred embodiment, the metal complex is a complex of metal rhodium, ruthenium, palladium or iridium.

[0048] In another preferred embodiment, the metal complex is a complex of phosphine-nitrogen ligand and iridium.

[0049] In another preferred embodiment, in step (b) or step (b'), when P is a benzyl or a p-methoxylbenzyl, benzyl or a p-methoxylbenzyl can be removed through catalytic hydrogenation by using a metal catalyst in an organic solvent under hydrogen atmosphere.

[0050] In another preferred embodiment, in step (b) or step (b'), when P is a silyl protecting group (such as tert-butyldimethylsilyl (TBDMS), tert-butyldiphenylsilyl (TBDPS)), P can be removed in an organic solvent by using tetrabutylammonium fluoride, cesium fluoride, potassium fluoride, hydrofluoric acid pyridine complex.

[0051] In another preferred embodiment, in step (b) or step (b'), when P is an alkyl protecting group, P can be removed in an organic solvent by using boron tribromide, boron trifluoride in diethyl ether.

[0052] The mole ratio of the compound of formula **3-P** (or the compound of formula **3-P-1**) to the metal complex catalyst is 10000: 1 - 10: 1, preferably 50: 1 - 100: 1.

[0053] The catalytic hydrogenation reaction is carried out under 1-100 normal atmospheric pressure of hydrogen at -78 - 80 °C for 1-48 hrs;
preferably, under 20-60 normal atmospheric pressure of hydrogen at 20 - 60 °C for 10-24 hrs.

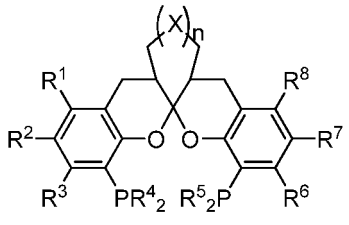
[0054] The compound of formula **4-P** (or the compound of formula **4-P-1**) is subjected to de-protection and then automatically ketalization, or is subjected to acidation by adding an acid and then ketalization, to form a chiral aromatic spiroketal compound. The acid is preferably hydrochloric acid, sulfuric acid, p-toluenesulfonic acid, phosphoric acid, acetic acid, trifluoroacetic acid, aluminium trichloride, boron trifluoride, iridium trichloride, copper trifluoromesylate, zinc trifluoromesylate, tin tetrachloride.

[0055] Said organic solvent is at least one of benzene, toluene, xylene, dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane, diethyl ether, tetrahydrofuran, methanol, ethanol, *N,N*-dimethyl formamide or dimethyl sulfoxide.

[0056] The Aromatic spiroketal compound prepared by above method can further be derived to prepare racemic or chiral aromatic spiroketal bisphosphine ligand to be used as a catalyst in asymmetric catalytic reaction.

Ligand

[0057] The ligand according to the present invention has a structure as shown in general formula I:



(I)

wherein R^1, R^2, R^3, R^6, R^7, R^8 are independently selected from a hydrogen, a halogen, substituted or unsubstituted following groups: a C_1-C_{10} alkyl, C_1-C_4 alkoxyl, a C_3-C_{30} cycloalkyl or an aryl;
R^4 and R^5 are independently selected from substituted or unsubstituted following groups: a C_3-C_{10} cycloalkyl, a C_1-C_{10} alkyl, 2-furyl or a phenyl; X is selected from CH_2, NH, NCH_3, O or S; n = 0-4;
wherein the substitution refers to be substituted by the following substituents: a halogen, a C_1-$_6$ alkyl, a C_1-$_6$ haloalkyl, or a C_1-$_6$ alkoxyl.

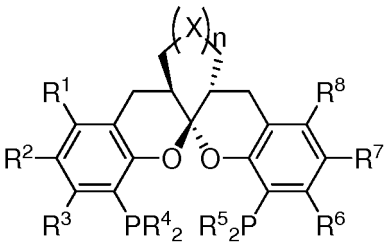
[0058] The additional condition is that not both of R^4 and R^5 are phenyl.

[0059] In another preferred embodiment, the aryl is selected from phenyl, phenylene, naphthyl, naphthalene, pyrenyl, anthryl, phenanthryl.

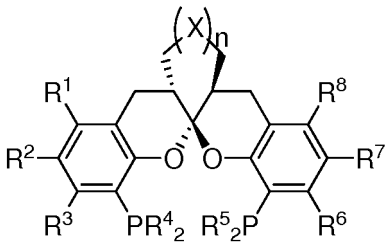
[0060] In another preferred embodiment, R^4 and R^5 are the same groups.

[0061] In another preferred embodiment, the substitution is mon-substituted, di-substituted or tri-substituted by the following substituents: a halogen, a C_1-$_6$ alkyl, a C_1-$_6$ haloalkyl, or a C_1-$_6$ alkoxyl.

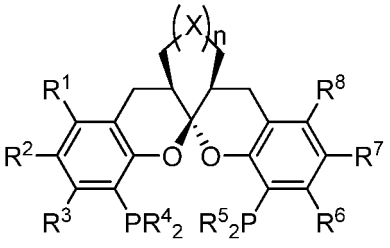
[0062] In another preferred embodiment, the ligand is a compound of formula Ia, a compound of formula Ib, a compound of formula Ic or a compound of formula Id with the following structures:



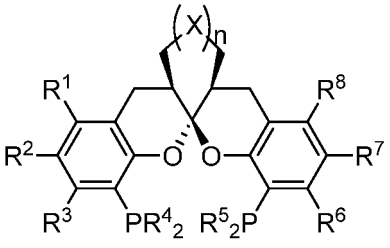
(Ia),



(Ib),



(Ic) or



(Id),

wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, X and n are defined as above.

[0063] In another preferred embodiment, the ligand contains a compound of formula Ia and a compound of formula Ib.

[0064] In another preferred embodiment, the ligand contains a compound of formula Ic and a compound of formula Id.

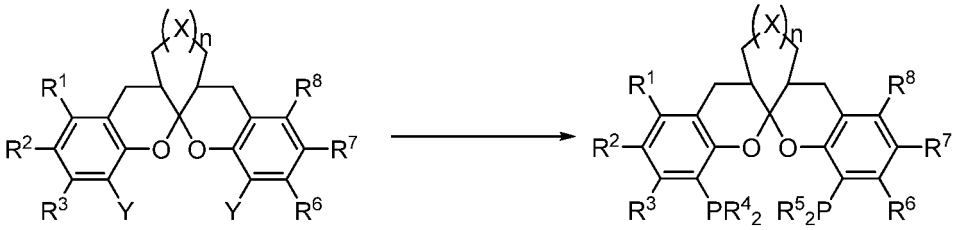
[0065] In another preferred embodiment, R^1, R^2, R^3, R^6, R^7 and R^8 are independently selected from a hydrogen, a C_1-C_6 alkyl, a C_1-C_4 alkoxyl, a C_3-C_{10} cycloalkyl, a phenyl or a halogen;
R^4 and R^5 are independently selected from a phenyl or a substituted phenyl, a C_3-C_6 cycloalkyl or a C_2-C_6 alkyl, and the substitution is mon-substituted, di-substituted or tri-substituted by the following substituents: a halogen, a C_1-$_6$ alkyl,

a C_{1-6} haloalkyl, or a C_{1-6} alkoxyl;
X is selected from CH_2, O, NCH_3 or S.

[0066] In another preferred embodiment, the ligand is any one selected from compounds of formulae 6b~6w, or enantiomers, racemates or diastereoisomers of the compounds of formulae 6b~6w. The racemate refers to a racemate composed of any one of the compounds of formulae 6b~6w and enantiomer thereof.

Preparation method

[0067] The preparation method for the ligand according to the present invention comprises the step of synthetizing the ligand from the compound of formula II,

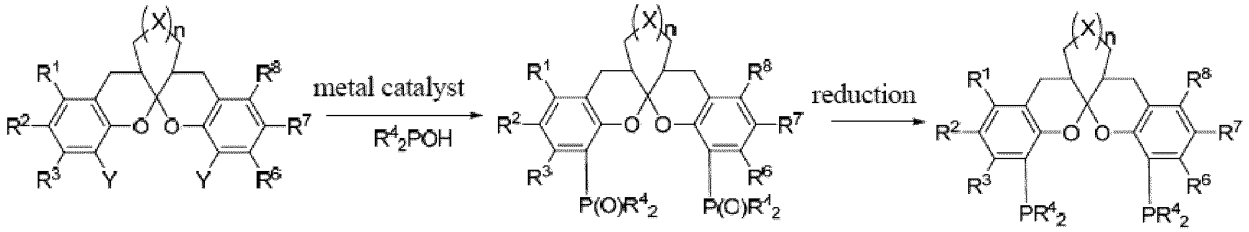


II I

wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, X and n are defiend as above, and Y is F, Cl, Br or I.

[0068] In another preferred embodiment, R^5 and R^4 are the same, and the method comprises the following steps:

(a1) the compound of formula II reacts with $R^4{}_2POH$ in an organic solvent under the action of a metal catalyst to form the compound of formula III;
(b1) the compound of formula III is reduced to obtain the ligand;



II III I

wherein Y is Cl, Br or I; R^1, R^2, R^3, R^4, R^6, R^7, R^8, X and n are defined as above.

[0069] In another preferred embodiment, said organic solvent is at least one of benzene, toluene, xylene, dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane, diethyl ether, tetrahydrofuran, methanol, ethanol, *N,N*-dimethyl formamide or dimethyl sulfoxide, or a mixture thereof.

[0070] In another preferred embodiment, the metal catalyst is at least one selected from $Pd(OAc)_2$, $PdCl_2$, $Pd_2(dba)_3$, $Pd(dba)_2$, $[Pd(C_3H_5)Cl]_2$, $Pd(PPh_3)_4$, $Pd(PPh_3)_2Cl_2$, $Pd(CH_3CN)Cl_2$, dpppNiCl$_2$, $Ni(PPh_3)_2Cl_2$, CuI or a combination thereof.

[0071] In another preferred embodiment, the metal catalyst is $Pd(OAc)_2$ or $Pd(PPh_3)_4$.

[0072] In another preferred embodiment, in step (a1), the mole ratio of the metal catalyst to the compound of formula II is 0.001 - 0.5: 1, and the mole ratio of $R^4{}_2POH$ to the compound of formula II is 2 - 10: 1.

[0073] In another preferred embodiment, the mole ratio of the metal catalyst to the compound of formula II in step (a1) is 0.005 - 0.1: 1, preferably 0.01 - 0.05: 1.

[0074] In another preferred embodiment, the mole ratio of $R^4{}_2POH$ to the compound of formula II in step (a1) is 2 - 6: 1, preferably, 2 - 3: 1.

[0075] In another preferred embodiment, the reaction temperature in step (a1) is 0 °C-150 °C, preferably, 60 °C - 100 °C. The reaction time is 1-48 hrs, preferably, 6-12 hrs.

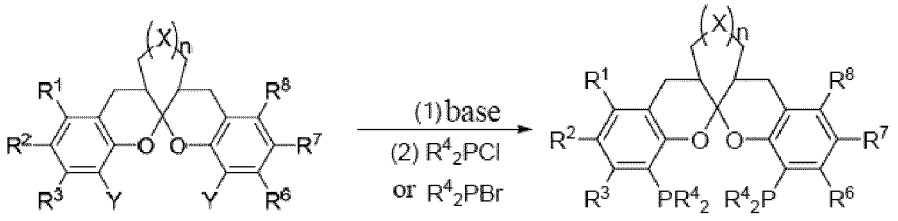
[0076] In another preferred embodiment, the reducing agent used in step (b1) is one selected from $HSiCl_3$, $(Me_2SiH)_2O$, $LiAlH_4$, $(EtO)_3SiH$ or a combination thereof.

[0077] In another preferred embodiment, the reducing agent is $HSiCl_3$.

[0078] In another preferred embodiment, the reaction temperature in step (b1) is 0 °C-150 °C. The reaction time is 1-48 hrs.

[0079] In another preferred embodiment, R^5 and R^4 are the same and the method comprises the steps:

(a2) Y group is removed from the compound of formula II and then the compound reacts with $R^4{}_2PCl$ or $R^4{}_2PBr$ in an organic solvent under the action of a base to obtain the ligand;



II I

wherein Y is Cl, Br or I; R^1, R^2, R^3, R^4, R^6, R^7, R^8, X and n are defined as above.

[0080] In another preferred embodiment, said organic solvent is at least one of benzene, toluene, xylene, dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane, diethyl ether, tetrahydrofuran, methanol, ethanol, *N,N*-dimethyl formamide or dimethyl sulfoxide, or a mixture thereof.

[0081] In another preferred embodiment, said base is selected from n-butyl lithium, tert-butyl lithium, cyclohexyl lithium, methyl lithium, isopropyl lithium, lithium bis(trimethylsilyl)amide, sodium bis(trimethylsilyl)amide, potassium bis(trimethylsilyl)amide, ethyl magnesium chloride, ethyl magnesium bromide, phenyl magnesium chloride, phenyl magnesium bromide.

[0082] In another preferred embodiment, said base is n-butyl lithium or tert-butyl lithium.

[0083] In another preferred embodiment, in step (a2), the mole ratio of the base to the compound of formula II is 2: 1 - 10: 1; and the mole ratio of $R^4{}_2PCl$ or $R^4{}_2PBr$ to the compound of formula II is 2: 1 - 10: 1.

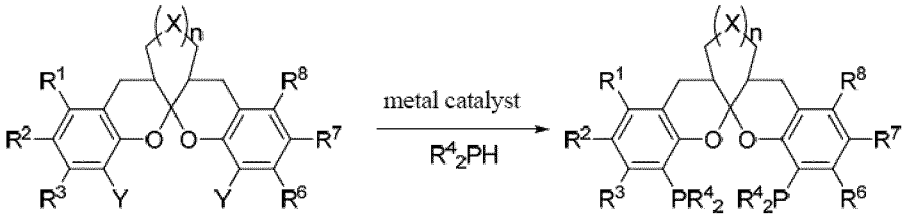
[0084] In another preferred embodiment, the mole ratio of the base to the compound of formula II in step (a2) is 2: 1 - 6: 1; preferably, 2: 1 - 3: 1.

[0085] In another preferred embodiment, the mole ratio of $R^4{}_2PCl$ or $R^4{}_2PBr$ to the compound of formula II in step (a2) is 2: 1 - 6: 1; preferably, 2: 1 - 3: 1.

[0086] In another preferred embodiment, in step (a2), the reaction temperature is -78°C - 100°C, preferably, -78°C - 60°C, more preferably, -78°C - 25°C, particularly preferably, -78°C - 0°C; and the reaction time is 0.5 hr - 48 hrs, preferably, 1 hr - 24 hrs.

[0087] In another preferred embodiment, R^5 and R^4 are the same, and the method comprises the steps:

(a3) under the action of a metal catalyst, the compound of formula II reacts with $R^4{}_2PH$ in an organic solvent to obtain the ligand;



II I

wherein Y is Cl, Br or I; and R^1, R^2, R^3, R^4, R^6, R^7, R^8, X and n are defined as above.

[0088] In another preferred embodiment, said organic solvent is at least one of benzene, toluene, xylene, dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane, diethyl ether, tetrahydrofuran, methanol, ethanol, *N,N*-dimethyl formamide or dimethyl sulfoxide, or a mixture thereof.

[0089] In another preferred embodiment, the metal catalyst is at least one selected from $Pd(OAc)_2$, $PdCl_2$, $Pd_2(dba)_3$, $Pd(dba)_2$, $[Pd(C_3H_5)Cl]_2$, $Pd(PPh_3)_4$, $Pd(PPh_3)_2Cl_2$, $Pd(CH_3CN)Cl_2$, dpppNiCl$_2$, $Ni(PPh_3)_2Cl_2$, CuI or a combination thereof.

[0090] In another preferred embodiment, the metal catalyst is $Pd(OAc)_2$ or $Pd(PPh_3)_4$.

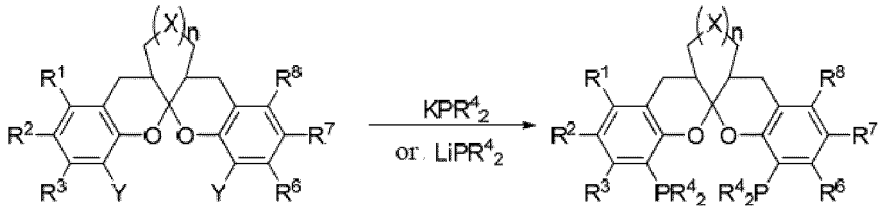
[0091] In another preferred embodiment, in step (a3), the mole ratio of the metal catalyst to the compound of formula II is 0.001 - 0.5: 1; and the mole ratio of $R^4{}_2PH$ to the compound of formula II is 2 - 10: 1.

[0092] In another preferred embodiment, the mole ratio of the metal catalyst to the compound of formula II in step (a3) is 0.005 - 0.1: 1, preferably, 0.01 - 0.05: 1.

[0093] In another preferred embodiment, the mole ratio of $R^4{}_2PH$ to the compound of formula II in step (a3) is 2 - 6: 1, preferably, 2~3:1.

[0094] In another preferred embodiment, in step (a3), the reaction temperature is 0 °C - 150 °C, preferably, 60 °C - 100 °C; and the reaction time is 1 hr - 48 hrs, preferably, 6 - 12 hrs.

[0095] In another preferred embodiment, R^5 and R^4 are the same, and the method comprises the steps:



II I

the compound of formula II reacts with $KPR^4{}_2$ or $LiPR^4{}_2$ in an organic solvent to form the ligand, wherein Y is F; and R^1, R^2, R^3, R^4, R^6, R^7, R^8, X and n are defined as above.

[0096] In another preferred embodiment, the mole ratio of $KPR^4{}_2$ or $LiPR^4{}_2$ to the compound of formula II is 2:1-10:1.

[0097] In another preferred embodiment, the mole ratio of $KPR^4{}_2$ or $LiPR^4{}_2$ to the compound of formula II is 2: 1 - 6: 1, preferably, 2: 1 - 3: 1.

[0098] In another preferred embodiment, $KPR^4{}_2$ or $LiPR^4{}_2$ can be prepared by corresponding phosphine compound and base on site.

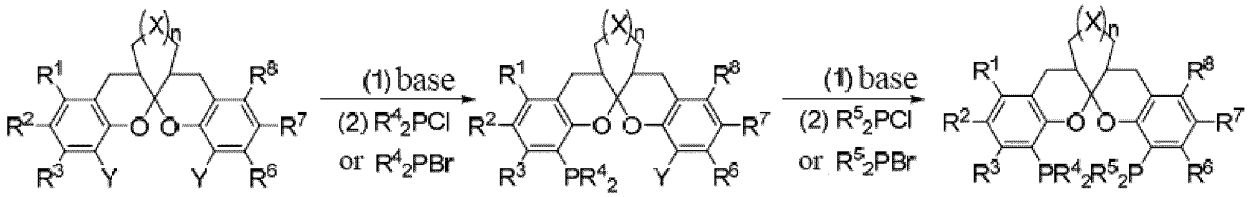
[0099] In another preferred embodiment, reaction temperature is -78 °C - 150 °C, preferably, 20 °C - 80 °C, and reaction time is 0.5 hr - 48 hrs, preferably, 6 - 10 hrs.

[0100] In another preferred embodiment, said organic solvent is at least one of benzene, toluene, xylene, dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane, diethyl ether, tetrahydrofuran, methanol, ethanol, *N,N*-dimethyl formamide or dimethyl sulfoxide, or a mixture thereof.

[0101] In another preferred embodiment, said base is selected from n-butyl lithium, tert-butyl lithium, cyclohexyl lithium, methyl lithium, isopropyl lithium, lithium bis(trimethylsilyl)amide, sodium bis(trimethylsilyl)amide, potassium bis(trimethylsilyl)amide, ethyl magnesium chloride, ethyl magnesium bromide, phenyl magnesium chloride, phenyl magnesium bromide.

[0102] In another preferred embodiment, said base is n-butyl lithium or tert-butyl lithium.

[0103] In another preferred embodiment, the method comprises the steps:



II IV I

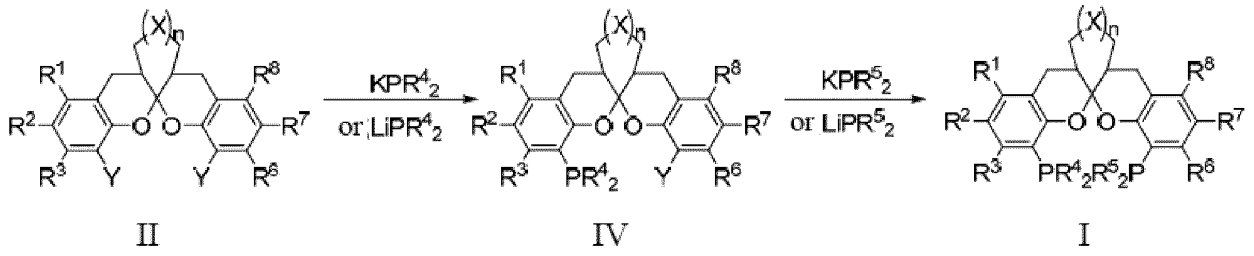
(i1) the compound of formula II reacts with a base in an organic solvent and then reacts with $R^4{}_2PCl$ or $R^4{}_2PBr$ to form a compound of formula IV;

(ii1) the compound of formula IV reacts with a base and then reacts with $R^5{}_2PCl$ or $R^5{}_2PBr$ to form the ligand,

wherein Y is Cl, Br or I;

R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, X and n are defined as above, and $R^4 \neq R^5$;

or comprises the steps:



II IV I

(i2) the compound of formula II reacts with KPR^4_2 or $LiPR^4_2$ in an organic solvent to form a compound of formula IV;
(ii2) the compound of formula IV reacts with KPR^5_2 or $LiPR^5_2$ to form the ligand,

wherein Y is F; R^1, R^2, R^3, R^4 R^5, R^6 R^7, R^8, R^9, R^{10}, X and n are defined as above, and $R^4 \neq R^5$.

[0104] In another preferred embodiment, in step (i1), the mole ratio of the base to the compound of formula II is 1: 1 - 1.2: 1; and the mole ratio of R^4_2PCl or R^4_2PBr to the compound of formula II is 1: 1 - 1.2: 1; and/or
in step (ii1), the mole ratio of the base to the compound of formula IV is 1: 1 - 1.2: 1; and the mole ratio of R^5_2PCl or R^5_2PBr to the compound of formula IV is 1: 1 - 1.2: 1.

[0105] In another preferred embodiment, reaction temperature is -78 °C - 100 °C, preferably, -78 °C - 60 °C, more preferably, -78 °C - 25 °C, particularly preferably, -78 °C - 0 °C; and the reaction time is 0.5 hr - 48 hrs, preferably, 1 hr - 24 hrs.

[0106] In another preferred embodiment, the mole ratio of KPR^4_2 or $LiPR^4_2$ to the compound of formula II in step (i2) is 1: 1 - 1.2: 1; and/or the mole ratio of KPR^5_2 or $LiPR^5_2$ to the compound of formula IV in step (ii2) is 1: 1 - 1.2: 1.

[0107] In another preferred embodiment, KPR^4_2, $LiPR^4_2$, KPR^5_2 or $LiPR^5_2$ can be prepared by corresponding phosphine compound and base on site.

[0108] In another preferred embodiment, the reaction temperature of step (i2) and (ii2) is -78 °C - 150 °C, preferably, 20 °C - 80 °C, and the reaction time is 0.5 hr - 48 hrs, preferably 6 - 10 hrs.

[0109] In another preferred embodiment, said organic solvent is one of benzene, toluene, xylene, dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane, diethyl ether, tetrahydrofuran, methanol, ethanol, *N,N*-dimethyl formamide or dimethyl sulfoxide, or a mixture thereof.

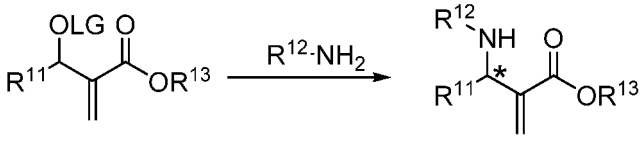
[0110] In another preferred embodiment, said base is selected from n-butyl lithium, tert-butyl lithium, cyclohexyl lithium, methyl lithium, isopropyl lithium, lithium bis(trimethylsilyl)amide, sodium bis(trimethylsilyl)amide, potassium bis(trimethylsilyl)amide, ethyl magnesium chloride, ethyl magnesium bromide, phenyl magnesium chloride, phenyl magnesium bromide.

[0111] In another preferred embodiment, said base is n-butyl lithium or tert-butyl lithium.

Use

[0112] The ligand according to the present invention can be used as a catalyst in asymmetric catalytic reaction. There is a ring system behind the spiroketalbackbone. The backbone can be effectively adjusted by changing ring system, thereby adjusting chiral-control ability of the ligand in different asymmetric catalytic reactions.

[0113] In one preferred embodiment, the ligand according to the present invention can form complex with a transition metal to be used as a catalyst in asymmetric allyl amination of Morita-Baylis-Hillman adduct, a compound of formula 8 to prepare a chiral α-alkylidene-β-amino carboxylic acid derivative, a compound of formula 9 with wide applications. The reaction equation is as follows:



8 9

wherein R^{11}, and R^{12} are independently selected from a phenyl, a substituted phenyl (for example, substituted by a halogen, a C_1-$_6$ alkyl, a C_1-$_6$ haloalkyl, or a C_1-$_6$ alkoxyl), 2-furyl, a C_3-C_{10} cycloalkyl or a C_1-C_{10} alkyl; R^{13} is selected from a methyl, an ethyl, an isopropyl, an n-butyl, a tert-butyl, a benzyl, or an adamantly; and LG is selected from an acetyl (Ac), a t-butyloxycarbonyl (Boc), a methoxycarbonyl (-CO_2Me) a di(ethoxy)phosphinyl ($POEt_2$).

[0114] The advantages of the invention include:

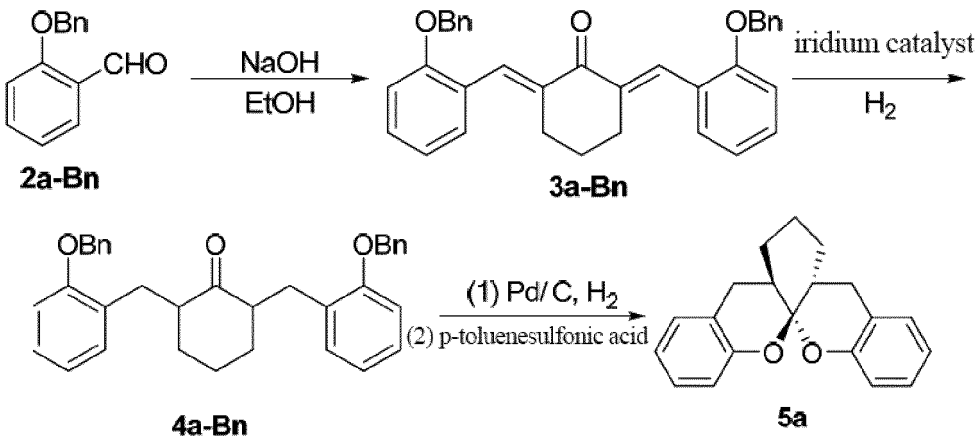
(1) the present invention provides a novel aromatic spiroketal bisphosphine ligand with optical activity which can be used as a catalyst in asymmetric catalytic reaction; and

(2) the present invention provides a simple and feasible preparation method for the aromatic spiroketal bisphosphine ligand which is racemic or possesses optical activity and can be prepared by a simple method from racemic and optically pure aromatic spiroketal compounds to obtain chiral ligands without resolution.

[0115] The invention will be further illustrated with reference to the following specific examples. It should be understood that these examples are only intended to illustrate the invention, but not to limit the scope of the invention. The experimental methods in the following examples without particular conditions mentioned are performed under routine conditions or as instructed by the manufacturer.

Example 1

[0116] The preparation method for the chiral aromatic spiroketal compound according to the present invention is illustrated by the preparation of chiral aromatic spiroketal compound **5a** from 3a-Bn (the reaction route is shown below) in this example.



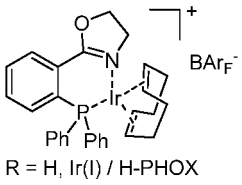
[0117] The first step: preparation of compound 3a-Bn from compound 2a-Bn

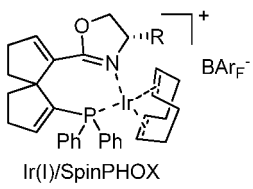
[0118] **2a-Bn** (4.0 g, 0.018 mol), cyclohexanone (0.93 mL, 0.009 mol), ethanol (10 mL) and 20% aqueous NaOH solution (5 mL) were added to a 250 mL one-necked flask and stirred at room temperature for 12 hrs. 100 mL of water was added and the reaction mixture was filtered to obtain yellow solids. After dried, yellow solids were recrystallized in a mixted solution of petroleum ether and ethyl acetate to obtain 3.5 g of yellow crystalline solids in 80% yield.

[0119] **3a-Bn,** yellow solid, ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.11 (s, 2H), 7.46-7.25 (s, 14H), 7.00-6.94 (m, 4H), 7.06-7.01 (m, 2H), 5.16 (s, 4H), 2.84 (t, J = 4.5 Hz, 4H), 1.76-1.74 (m, 4H) ppm.

[0120] The second step: preparation of compound **4a-Bn** from compound **3a-Bn**

[0121] The hydrogenation product, **4a-Bn** was prepared by using compound **3a-Bn** as a hydrogenation substrate and different phosphine-oxazoline ligands-iridium complex as catalysts. The reaction was conducted as follows: **3a-Bn** (48 mg, 0.1 mmol), iridium complex (0.001 mmol) and 2 mL of anhydrous dichloromethane were added to a hydrogenation flask. The hydrogenation flask was placed in a glovebox and transferred to a high pressure reactor. Hydrogen displacement was performed for three times, and then the reactor was charged with 50 atm of hydrogen. The reaction was carried out at room temperature for 24 hrs. After hydrogen was discharged, the reactor was opened and the solvent was removed under reduced pressure. The ratio of cis-form to trans-form of the product was determined by crude ^{1}H-NMR. The residue was separated by column chromatography. The yield of trans-**4a-Bn** was obtained and enantioselectivity was determined by chiral high pressure liquid chromatography.





R = ^{t}Bu, (*R,S*)-**7a** (*S,S*)-**7a**
R = ^{s}Bu, (*R,S*)-**7b** (*S,S*)-**7b**
R = Bn, (*R,S*)-**7c** (*S,S*)-**7c**
R = ^{i}Pr, (*R,S*)-**7d** (*S,S*)-**7d**
R = Ph, (*R,S*)-**7e** (*S,S*)-**7e**

Table 1: asymmetric hydrogenation results of substrate **3a-Bn** by using different phosphine-oxazoline ligands-iridium complex as catalysts

catalyst	yield of trans-**4a-Bn** compound (%)	trans/cis	ee(%) (trans-**4a-Bn** compound)
Ir(I)/(*R,S*)-**7a**	83	91/9	> 99 (-)
Ir(I)/(*S,S*)-**7a**	77	83/17	> 99 (+)
Ir(I)/(*R,S*)-**7b**	45	56/44	98 (-)
Ir(I)/(*S,S*)-**7b**	81	84/16	> 99 (+)
Ir(I)/(*R,S*)-**7c**	80	82/18	> 99 (-)
Ir(I)/(*S,S*)-**7c**	89	93/7	> 99 (+)
Ir(I)/(*R,S*)-**7d**	65	68/31	> 99 (-)
Ir(I)/(*S,S*)-**7d**	87	ND	ND (+)
Ir(I)/(*R,S*)-**7e**	89	91/9	> 99 (-)
Ir(I)/(*R,S*)-**7e**	88	90/10	> 99 (+)
note: iridium complex used was prepared according to the method reported in Angew. Chem. Int. Ed. 2009, 48, 5345.			

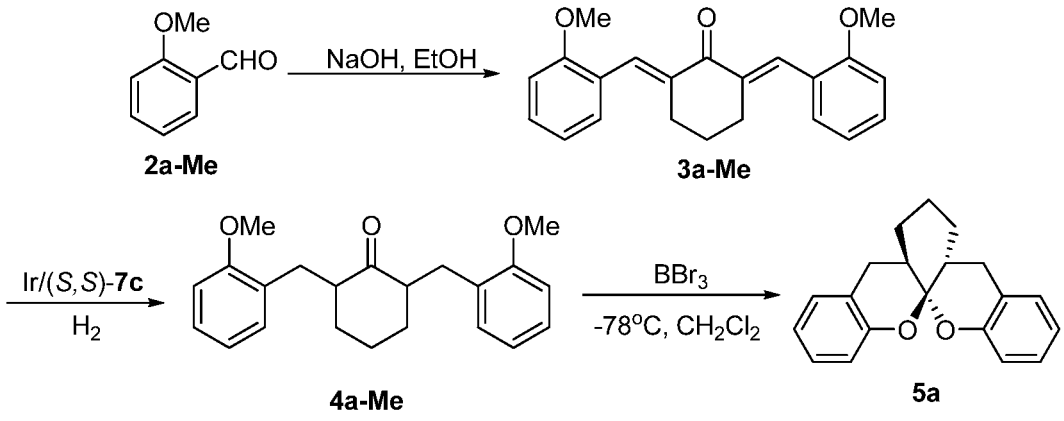
[0122] Results from Ir(I)/(*S,S*)-**7c** used as the catalyst: **4a-Bn,** viscous liquid, $[\alpha]_D^{20}$ = + 28.6 (*c* 1.00, $CHCl_3$), >99% ee (determined by high performance liquid chromatography, chiral AD-H column, n-hexane/isopropyl alcohol = 99 : 1, 1.0 mL/min, 230 nm; t_R (major) = 5.69 min; t_R (minor) = 6.82 min). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41-7.22 (m, 10H), 7.17-7.12 (m, 2H), 7.02 (d, J = Hz, 2H), 6.89-6.79 (m, 4H), 5.05 (s, 4H), 3.07 (dd, *J* = 13.5, 5.7 Hz, 2H), 2.94-2.90 (m, 2H), 2.68 (dd, *J* = 13.2, 9.0 Hz, 2H), 1.84-1.52 (m, 6H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 215.2, 156.4, 137.1, 130.8, 128.9, 128.3, 127.6, 127.2, 126.8, 120.4, 111.4, 69.5, 48.8, 32.1, 30.8, 20.4 ppm.

The third step: preparation of compound **5a** from compound **4a-Bn**

[0123] Compound **4a-Bn** was used as a substrate and benzyl was removed by using Pd/C as a catalyst under hydrogen atmosphere to prepare compound **5a**. The reaction was conducted as follows: **4a-Bn** (80 mg, 0.16mmol), Pd/C (10 mg) and 2 mL of methanol were added to a hydrogenation flask and then transferred to a high pressure reactor in air. Hydrogen displacement was performed for three times, and then the reactor was charged with 5 atm of hydrogen. The reaction was carried out at room temperature for 24 hrs. After hydrogen was discharged, the reactor was opened, and p-toluenesulfonic acid (10 mg) was added and then stirred at room temperature for 2 hrs. The solvent was removed under reduced pressure and the residue was separated by column chromatography to obtain trans-**5a** in 90% yield. The ee value of trans-**5a** is more than 99% and absolute configuration is (*R,R,R*).

Example 2

[0124] The preparation method for the chiral aromatic spiroketal compound according to the present invention is illustrated by the preparation of chiral aromatic spiroketal compound **5a** from **3a-Me** (the reaction route is shown below) in this example.



The first step: preparation of compound **3a-Me** from compound **2a-Me**

[0125] **2a-Me** (2.44g, 0.018mol), cyclohexanone (0.93 mL, 0.009 mol), ethanol (10 mL) and 20% aqueous NaOH solution (5 mL) were added to a 250 mL one-necked flask and stirred at room temperature for 12 hrs. 100 mL of water was added and the reaction mixture was filtered to obtain yellow solids. After dried, yellow solids were recrystallized in a mixted solution of petroleum ether and ethyl acetate to obtain 2.5 g of yellow crystalline solids in 83% yield.

[0126] **3a-Me,** yellow solid, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (s, 2H), 7.32-7.28 (m, 4H), 6.97-6.89 (m, 4H), 3.84 (s, 6H), 2.84-2.80 (m, 4H), 1.76-1.70 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.4, 158.2, 136.4, 132.3, 130.2, 129.9, 125.0, 119.8, 110.5, 55.3, 28.6, 23.4 ppm.

The third step: preparation of compound **4a-Me** from compound **3a-Me**

[0127] The hydrogenation product **4a-Me** was prepared by using compound **3a-Me** as a hydrogenation substrate and Ir(I)/(*S,S*)-**7c** as a catalyst. The reaction was conducted as follows: **3a-Me** (33.4 mg, 0.1mmol), Ir(I)/(*S,S*)-**7c** (1.6 mg, 0.001 mmol) and 2 mL of anhydrous dichloromethane were added to a hydrogenation flask. The hydrogenation flask was placed in glovebox and transferred to a high pressure reactor. Hydrogen displacement was performed for three times, and then the reactor was charged with 50 atm of hydrogen. The reaction was carried out at room temperature for 24 hrs. After hydrogen was discharged, the reactor was opened and the solvent was removed under reduced pressure. The ratio of cis-form to trans-form of the product was determined by crude ^{1}H-NMR. The residue was separated by column chromatography. The yield of trans**-4a-Me** was 90%, the ratio of trans-form to cis-form was 94/6 and the ee value of trans**-4a-Me** was more than 99%.

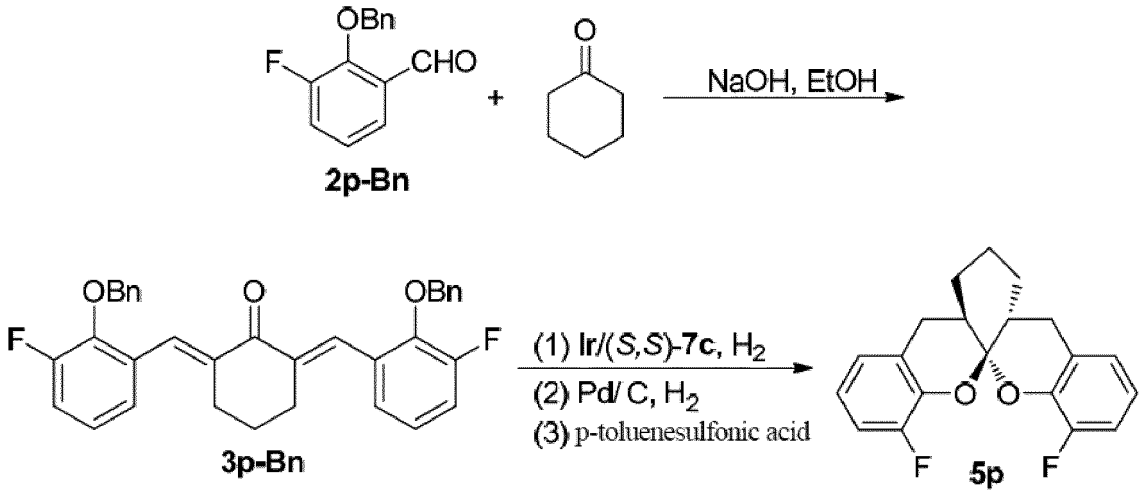
[0128] **4a-Me,** viscous liquid, $[\alpha]_D^{20}$ = +14.1 (*c* 1.00, $CHCl_3$), >99% ee (determined by high performance liquid chromatography, chiral OD-H column; n-hexane/isopropyl alcohol = 90 : 10, 1.0 mL/min, 220 nm; t_R (major) = 7.97 min; t_R (minor) = 9.45 min). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.16 (t, *J* = 7.8 Hz, 2H), 7.05 (d, *J* = 7.5 Hz, 2H), 6.86-6.80 (m, 4H), 3.77 (s, 6H), 3.11 (dd, *J* = 13.5, 6.3 Hz, 2H), 2.90-2.85 (m, 2H), 2.62 (dd, *J* = 13.5, 8.4 Hz, 2H), 1.86-1.69 (m, 4H), 1.59-1.53 (m, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 215.3, 157.3, 130.6, 128.0, 127.2, 120.1, 110.1, 54.9, 48.9, 32.5, 30.9, 20.4 ppm.

The third step: preparation of compound **5a** from compound **4a-Me**

[0129] The substrate **4a-Me** (110 mg, 0.32 mmol), anhydrous N,N-dimethylformamide (2 mL) and sodium thioethylate (60 mg, 0.704 mmol) were added to a 10 mL of water-free and oxygen-free Schlenk tube and heated to reflux for 5 hrs. The reaction mixture was cooled to room temperature and p-toluenesulfonic acid (20 mg) was added and stirred at room temperature for 1.5 hrs. 5 mL of saturated sodium bicarbonate was added to quench the reaction and the reaction mixture was extraced with dichloromethane for three times, dried on anhydrous sodium sulfate, filtered and concentrated. The residue was separated by column chromatography to obtain **5a** in 78% yield, the ee value of which was more than 99%.

Example 3

[0130] The preparation method for the chiral aromatic spiroketal compound according to the present invention is illustrated by the preparation of chiral aromatic spiroketal compound **5p** from **3p-Bn** (the reaction route is shown below) in this example.



[0131] The first step: preparation of compound **3p-Bn** from compound **2p-Bn**

[0132] **2p-Bn** (4.14g, 0.018mol), cyclohexanone (0.93 mL, 0.009 mol), ethanol (10 mL) and 20% aqueous NaOH solution (5 mL) were added to a 250 mL one-necked flask and stirred at room temperature for 12 hrs. 100 mL of water was added and the reaction mixture was filtered to obtain yellow solids. After dried, yellow solids were recrystallized in a mixted solution of petroleum ether and ethyl acetate to obtain 3.8 g of yellow crystalline solids in 80.8% yield.

[0133] **3p-Bn,** yellow solid, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87, 7.42-7.39 (m, 4H), 7.33-7.27 (m, 6H), 7.10-6.98 (m, 6H), 5.08 (s, 4H), 2.68-2.64 (m, 4H), 1.64-1.58 (m, 2H) ppm; ^{19}F NMR (368 MHz, $CDCl_3$) δ -129.1 ppm.

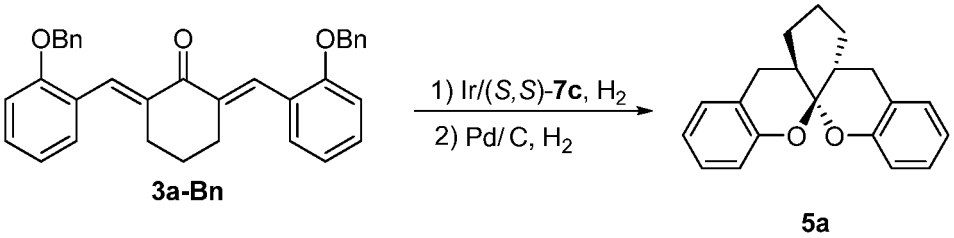
[0134] The second step: preparation of compound **5p** from compound **3p-Bn**

[0135] The compound **4p** was prepared by using compound **3p-Bn** as a hydrogenation substrate and Ir(I)/(*S,S*)-**7c** as a catalyst. The reaction was conducted as follows: **3p-Bn** (52 mg, 0.1mmol), Ir(I)/(*S,S*)-**7c** (1.6mg, 0.001mmol) and 2 mL of anhydrous dichloromethane were added to a hydrogenation flask. The hydrogenation flask was placed in a glovebox and transferred to a high pressure reactor. Hydrogen displacement was performed for three times, and then the reactor was charged with 50 atm of hydrogen. The reaction was carried out at room temperature for 6 hrs. After hydrogen was discharged, the reactor was opened and the solvent was removed under reduced pressure. After the catalyst was removed by a short silica column, the obtained viscous liquid was directly added to a hydrogenation flask. 10 mg Pd/C and 4 mL of methanol were added and the hydrogenation flask was placed in a reactor. The reactor was charged with 5 atm of hydrogen and the reaction was carried out for 10 hrs. After hydrogen was discharged, p-toluenesulfonic acid (10 mg) was directly added to the hydrogenation flask and stirred at room temperature for 2 hrs. After filtered and concentrated, the residue was separated by column chromatography. The yield of trans-**5p** was 90%, the ratio of trans-form to cis-form was 93/7, the ee value of trans-**5p** was more than 99% and absolute configuration was *(R,R,R).*

[0136] **5p**, white solid, mp 160-161°C, $[\alpha]_D^{20}$ = -33.1 *(c* 1.00, $CHCl_3$), >99% ee (determined by high performance liquid chromatography, chiral AD-H column, n-hexane/isopropyl alcohol = 90 : 10, 1.0 mL/min, 230 nm; t_R (minor) = 4.99 min; t_R (major) = 7.57 min). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.21-7.19 (m, 4H), 6.71 (d, *J* = 9.0 Hz, 2H), 2.90 (dd, *J* = 16.5, 6.0 Hz, 2H), 2.65 (dd, *J* = 17.1, 7.5 Hz, 2H), 2.29-2.26 (m, 2H), 1.83-1.77 (m, 2H), 1.61-1.47 (m, 4H) ppm; ^{19}F NMR (282 MHz, $CDCl_3$) δ 121.8 ppm.

Example 4

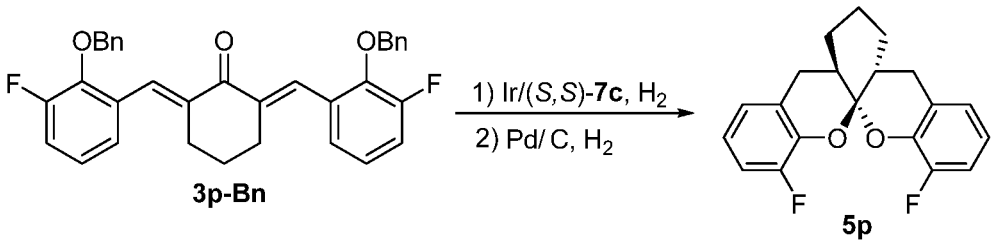
[0137] The one-pot preparation method for the chiral aromatic spiroketal compound according to the present invention is illustrated by the preparation of chiral aromatic spiroketal compound **5a** from **3a-Bn** (the reaction route is shown below) in this example.



[0138] Compound **3a-Bn** was used as a hydrogenation substrate and Ir(I)/(*S,S*)-**7c** was used as a catalyst. The reaction was conducted as follows: **3a-Bn** (48 mg, 0.1mmol), Ir(I)/(S,S)-7c(1.6mg, 0.001mmol) and 2 mL of anhydrous dichloromethane were added to a hydrogenation flask. The hydrogenation flask was placed in a glovebox and transferred to a high pressure reactor. Hydrogen displacement was performed for three times, and then the reactor was charged with 50 atm of hydrogen. The reaction was carried out at room temperature for 6 hrs. After hydrogen was discharged, the reactor was opened and Pd/C (10 mg) was directly added to the hydrogenation flask which was then transferred to a high pressure reactor in air. Hydrogen displacement was performed for three times, and then the reactor was charged with 5 atm of hydrogen. The reaction was carried out at room temperature for 24 hrs. After hydrogen was discharged, the reactor was opened and the solvent was removed under reduced pressure. The ratio of cis-form to trans-form of the product was determined by crude ^{1}H-NMR. The residue was separated by column chromatography. The yield of trans-**5a** was 88%, the ratio of trans-form to cis-form was 92/8, the ee value of trans-**5a** was more than 99% and absolute configuration was *(R,R,R).*

Example 5

[0139] The one-pot preparation method for the chiral aromatic spiroketal compound according to the present invention is illustrated by the preparation of chiral aromatic spiroketal compound **5p** from **3p-Bn** (the reaction route is shown below) in this example.

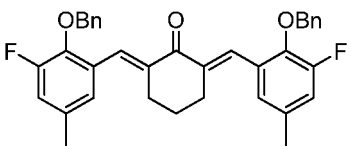


3p-Bn **5p**

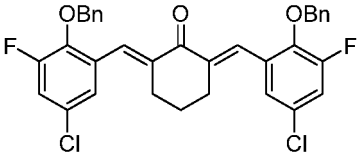
[0140] Compound **3p-Bn** was used as a hydrogenation substrate and Ir(I)/(*S,S*)-**7c** was used as a catalyst. The reaction was conducted as follows: **3p-Bn** (52 mg, 0.1 mmol), Ir(I)/(*S,S*)-**7c** (1.6 mg, 0.001 mmol) and 2 mL of anhydrous dichloromethane were added to a hydrogenation flask. The hydrogenation flask was placed in a glovebox and transferred to a high pressure reactor. Hydrogen displacement was performed for three times, and then the reactor was charged with 50 atm of hydrogen. The reaction was carried out at room temperature for 6 hrs. After hydrogen was discharged, the reactor was opened and 10 mg of Pd/C was directly added to the hydrogenation flask which was then placed in a reactor. The reactor was charged with 5 atm of hydrogen and the reaction was carried out for 10 hrs. After hydrogen was discharged, the reaction mixture was filtered and concentrated and the residue was separated by column chromatography to obtain trans-**5p** in 91% yield. The ratio of trans-form to cis-form was 92/8, the ee value of trans-**5p** was more than 99% and absolute configuration was (*R,R,R*).

Example 6

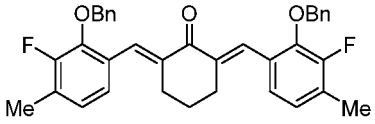
[0141] Compounds of Formulae **3b-Bn - 3i-Bn** were prepared according to the method of example 1 by using benzyl-protecting 3-fluoro-5-methylsalicylaldehyde, 3-fluoro-5-chlorosalicylaldehyde, 3-fluoro-4-methylsalicylaldehyde, 3-benzyloxysalicylaldehyde, 5-methylsalicylaldehyde, 4-methoxysalicylaldehyde to replace benzyl-protecting salicylaldehyde, respectively.



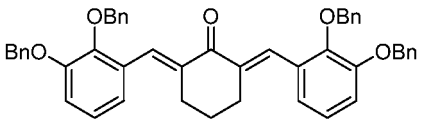
3b-Bn



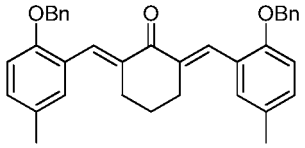
3c-Bn



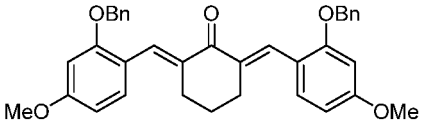
3d-Bn



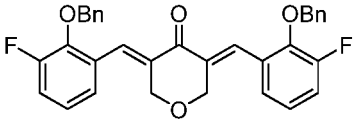
3e-Bn



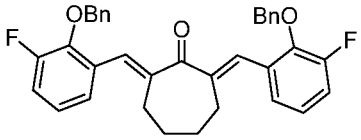
3f-Bn



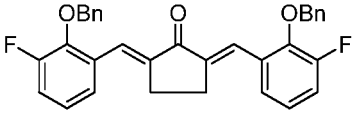
3g-Bn



3h-Bn



3i-Bn



3j-Bn

3b-Bn, ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (s, 2H), 7.31-7.26 (m, 8H), 7.11-7.09 (m, 2H), 7.05-6.81 (m, 4H), 5.15 (s, 4H), 2.82 (t, *J* = 4.8Hz, 4H), 2.32 (s, 6H), 1.75-1.71 (m, 2H) ppm. ^{19}F NMR (282 MHz, $CDCl_3$) δ 123.6 ppm.

3c-Bn, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (s, 2H), 7.38-7.21 (m, 10H), 7.07-6.92 (m, 4H), 5.19 (s, 4H), 2.88-2.69 (m, 4H), 1.69-1.58 (m, 2H) ppm. ^{19}F NMR (282 MHz, $CDCl_3$) δ 125.6ppm.

3d-Bn, ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (s, 2H), 7.38-7.27 (m, 8H), 7.09-7.06 (m, 2H), 7.01-6.71 (m, 4H), 5.04 (s, 4H), 2.81-2.78 (m, 4H), 2.33 (s, 6H), 1.77-1.72 (m, 2H) ppm. ^{19}F NMR (282 MHz, $CDCl_3$) δ 127.9 ppm.

3e-Bn, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (s, 2H), 7.48-7.21 (m, 20H), 7.05-6.90 (m, 6H), 5.14 (s, 4H), 5.01 (s, 4H), 2.71-2.64 (m, 4H), 1.63-1.57 (m, 2H) ppm.

3f-Bn, ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (s, 2H), 7.42-7.28 (m, 10H), 7.13 (s, 2H), 7.06-7.04 (m, 2H), 6.83 (d, *J* = 8.4Hz, 2H), 5.11 (s, 4H), 2.83 (t, *J* = 5.2Hz, 4H), 2.29 (s, 6H), 1.76-1.70 (m, 2H) ppm.

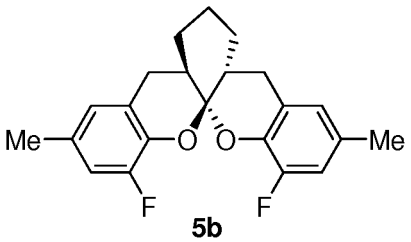
3g-Bn, ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07(s, 2H), 7.47-7.27 (m, 12H), 6.53-6.49 (m, 4H), 5.13 (s, 4H), 3.79 (s, 6H), 2.87-2.81 (m, 4H), 1.80-1.71 (m, 2H) ppm.

3h-Bn, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (s, 2H), 7.63-7.52 (m, 10H), 7.45-7.31 (m, 2H), 6.90-6.82 (m, 4H), 5.15 (s, 4H), 4.81 (s, 4H) ppm; ^{19}F NMR (282 MHz, $CDCl_3$) δ 126.2 ppm.

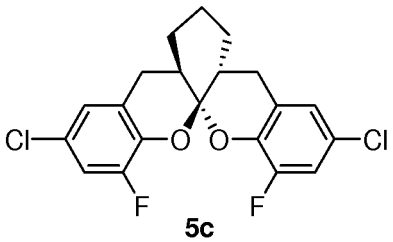
3i-Bn, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (s, 2H), 7.45-7.32 (m, 8H), 7.24-7.17 (m, 4H), 6.90-6.83 (m, 4H), 5.19 (s, 4H), 2.78-2.68 (m, 4H), 1.97-1.82 (m, 4H) ppm; ^{19}F NMR (282 MHz, $CDCl_3$) δ 125.3 ppm.

3j-Bn, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (s, 2H), 7.54-7.38 (m, 10H), 6.89-6.78 (m, 2H), 6.65-6.60 (m, 4H), 5.20 (s, 4H), 2.69-2.78 (m, 4H) ppm; ^{19}F NMR (282 MHz, $CDCl_3$) δ 124.2 ppm.

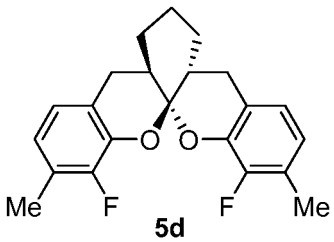
[0142] The preparation method for the following compounds were described in detail by the following exampls.



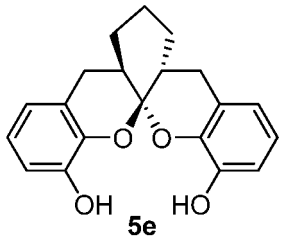
5b



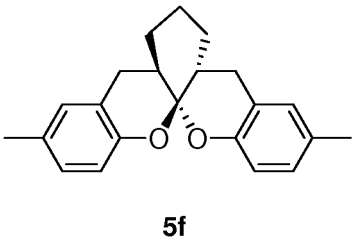
5c



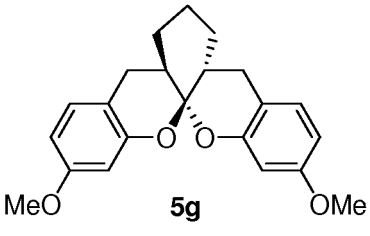
5d



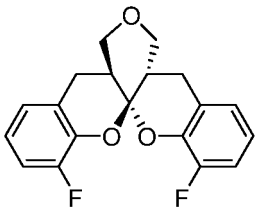
5e



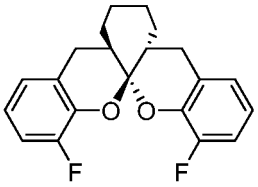
5f



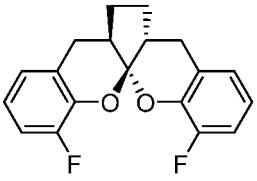
5g



5h



5i



5j

Example 7

[0143] Compound **3b-Bn** prepared in example 6 was used as a hydrogenation substrate and compound Ir(I)/(*S,S*)-**7c** was used as a catalyst to prepare chiral aromatic spiroketal compound (*R,R,R*)**-5b**. The reaction was conducted as follows: **3b-Bn** (275mg, 0.5mmol), catalyst Ir(I)/(*S,S*)-**7c** (4.8mg, 0.003mmol) and 10 mL of anhydrous dichloromethane were added to a hydrogenation flask. The hydrogenation flask was placed in a glovebox and transferred to a high pressure reactor. Hydrogen displacement was performed for three times, and then the reactor was charged with 50 atm of hydrogen. The reaction was carried out at room temperature for 6 hrs. After hydrogen was discharged, the reactor was opened and 20 mg of Pd/C was directly added to the hydrogenation flask which was then placed in a reactor. The reactor was charged with 5 atm of hydrogen and the reaction was carried out for 10 hrs. After hydrogen was discharged, the reaction mixture was filtered and concentrated and the residue was separated by column chromatography to obtain (*R,R,R*)-**5b** in 87% yield, the ee value of which was more than 99%. (*R,R,R*)-**5b**, $[\alpha]_D^{20}$ = -97.8 (*c* 1.0, $CHCl_3$), >99% ee (determined by high performance liquid chromatography, chiral AD-H column; n-hexane/isobutanol = 99 : 1, 1.0 mL/min, 230 nm; t_R (major) = 4.87 min; t_R (minor) = 6.52 min). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15 (s, 2H), 6.81 (s, 2H), 2.95 (dd, *J* = 16.2, 6.0 Hz, 2H), 2.68(dd, *J* = 16.6, 7.2 Hz, 2H), 2.38-2.32 (m, 2H), 2.25 (s, 6H), 1.85-1.78 (m, 2H), 1.58-1.47 (m, 4H) ppm; ^{19}F NMR (282 MHz, $CDCl_3$) δ 123.5 ppm.

Example 8

[0144] Compound **3c-Bn** prepared in example 6 was used as a hydrogenation substrate and compound Ir(I)/(*R,S*)-**7e** was used as a catalyst to prepare chiral aromatic spiroketal compound (*R,R,R*)**-5c**. The reaction was conducted as follows: **3c-Bn** (295 mg, 0.5mmol), catalyst Ir(I)/(*R,S*)-**7e** (4.8mg, 0.003mmol) and 10 mL of anhydrous dichloromethane were added to a hydrogenation flask. The hydrogenation flask was placed in a glovebox and transferred to a high pressure reactor. Hydrogen displacement was performed for three times, and then the reactor was charged with 50 atm of hydrogen. The reaction was carried out at room temperature for 6 hrs. After hydrogen was discharged, the reactor was opened and 20 mg of Pd/C was directly added to the hydrogenation flask which was then placed in a reactor. The reactor was charged with 5 atm of hydrogen and the reaction was carried out for 10 hrs. After hydrogen was discharged, the reaction mixture was filtered and concentrated and the residue was separated by column chromatography to obtain (*R,R,R*)**-5c** in 89% yield, the ee value of which was more than 99%.

[0145] (*R,R,R*)-**5c**, $[\alpha]_D^{20}$ = -77.2 (*c* 1.20, $CHCl_3$), >99% ee (determined by high performance liquid chromatography, chiral AD-H column; n-hexane/isobutanol = 99 : 1, 1.0 mL/min, 230 nm; t_R (major) = 6.68 min; t_R (minor) = 6.98 min). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (d, *J* = 2.6 Hz, 2H), 7.06 (d, *J* = 2.6 Hz, 2H), 3.03 (dd, *J* = 16.4 Hz, 6.2 Hz, 2H), 2.68 (dd, *J* = 16.6 Hz, 7.8 Hz, 2H), 2.35-2.33 (m, 2H), 1.86-1.81 (m, 2H), 1.64-1.48 (m, 4H) ppm; ^{19}F NMR (282 MHz, $CDCl_3$) δ 125.7 ppm.

Example 9

[0146] Compound **3d-Bn** prepared in example 6 was used as a hydrogenation substrate and compound Ir(I)/(*R,S*)-**7e** was used as a catalyst to prepare chiral aromatic spiroketal compound (R,R,R)-5d. The reaction was conducted as

follows: **3d-Bn** (275 mg, 0.5mmol), catalyst Ir(I)/(*R,S*)-**7e** (4.8mg, 0.003mmol) and 10 mL of anhydrous dichloromethane were added to a hydrogenation flask. The hydrogenation flask was placed in a glovebox and transferred to a high pressure reactor. Hydrogen displacement was performed for three times, and then the reactor was charged with 50 atm of hydrogen. The reaction was carried out at room temperature for 6 hrs. After hydrogen was discharged, the reactor was opened and 20 mg of Pd/C was directly added to the hydrogenation flask which was then placed in a reactor. The reactor was charged with 5 atm of hydrogen and the reaction was carried out for 10 hrs. After hydrogen was discharged, the reaction mixture was filtered and concentrated and the residue was separated by column chromatography to obtain (*R,R,R*)-**5d** in 92% yield, the ee value of which was more than 99%.

[0147] (*R,R,R*)-**5d**, $[\alpha]_D^{20}$ = -81.2 (*c* 1.10, $CHCl_3$), >99% ee (determined by high performance liquid chromatography, chiral AD-H column; n-hexane/isobutanol = 99 : 1, 1.0 mL/min, 230 nm; t_R (major) = 5.65 min; t_R (minor) = 6.25 min). ^1H NMR (400 MHz, $CDCl_3$) δ 7.36 (d, *J* = 2.6 Hz, 2H), 7.13 (d, *J* = 2.4 Hz, 2H), 3.12 (dd, *J* = 16.8 Hz, 6.6 Hz, 2H), 2.62 (dd, *J* = 16.8 Hz, 7.9 Hz, 2H), 2.38-2.31 (m, 2H), 1.89-1.81 (m, 2H), 1.68-1.49 (m, 4H) ppm; ^{19}F NMR (282 MHz, $CDCl_3$) δ 129.1 ppm.

Example 10

[0148] Compound **3e-Bn** prepared in example 6 was used as a hydrogenation substrate and compound Ir(I)/(*S,S*)-**7e** was used as a catalyst to prepare chiral aromatic spiroketal compound (*R,R,R*)-**5e**. The reaction was conducted as follows: **3e-Bn** (349.4 mg, 0.5mmol), catalyst Ir(I)/(*S,S*)-**7e** (4.8mg, 0.003 mmol) and 10 mL of anhydrous dichloromethane were added to a hydrogenation flask. The hydrogenation flask was placed in a glovebox and transferred to a high pressure reactor. Hydrogen displacement was performed for three times, and then the reactor was charged with 50 atm of hydrogen. The reaction was carried out at room temperature for 6 hrs. After hydrogen was discharged, the reactor was opened and 20 mg of Pd/C was directly added to the hydrogenation flask which was then placed in a reactor. The reactor was charged with 5 atm of hydrogen and the reaction was carried out for 10 hrs. After hydrogen was discharged, the reaction mixture was filtered and concentrated and the residue was separated by column chromatography to obtain (*R,R,R*)-**5e** in 86% yield, the ee value of which was more than 99%.

[0149] *(R,R,R)-5e,* $[\alpha]_D^{20}$ = -99.2 (*c* 1.00, $CHCl_3$), >99% ee (determined by high performance liquid chromatography, chiral AD-H column; n-hexane/isobutanol = 90 : 10, 1.0 mL/min, 230 nm; t_R (major) = 6.46 min; t_R (minor) = 6.98 min). 1H NMR (400 MHz, $CDCl_3$) δ 6.86-6.75 (m, 4H), 6.67-6.63 (m, 2H), 5.42 (s, 2H), 2.99-2.89 (m, 2H), 2.79-2.68 (m, 2H), 2.44-2.34 (m, 2H),1.90-1.78 (m, 2H), 1.68-1.52 (m, 4H) ppm.

Example 11

[0150] Compound **3f-Bn** prepared in example 6 was used as a hydrogenation substrate and compound Ir(I)/(*S,S*)-**7a** was used as a catalyst to prepare chiral aromatic spiroketal compound (*R,R,R*)-**5f**. The reaction was conducted as follows: **3f-Bn** (257 mg, 0.5 mmol), catalyst Ir(I)/(*S,S*)-**7a** (4.8 mg, 0.003 mmol) and 10 mL of anhydrous dichloromethane were added to a hydrogenation flask. The hydrogenation flask was placed in a glovebox and transferred to a high pressure reactor. Hydrogen displacement was performed for three times, and then the reactor was charged with 50 atm of hydrogen. The reaction was carried out at room temperature for 6 hrs. After hydrogen was discharged, the reactor was opened and 20 mg of Pd/C was directly added to the hydrogenation flask which was then placed in a reactor. The reactor was charged with 5 atm of hydrogen and the reaction was carried out for 10 hrs. After hydrogen was discharged, the reaction mixture was filtered and concentrated and the residue was separated by column chromatography to obtain (*R,R,R*)-**5f** in 77% yield, the ee value of which was more than 99%.

[0151] (*R,R,R*)-**5f**, $[\alpha]_D^{20}$ = -37.9 (*c* 1.00, $CHCl_3$), >99% ee (determined by high performance liquid chromatography, chiral AD-H column, n-Hex/i-PrOH = 90 : 10, 1.0 mL/min, 230 nm; t_R (minor) = 4.43 min; t_R (major) = 10.20 min). ^1H NMR (400 MHz, $CDCl_3$) δ 6.91-6.88 (m, 4H), 6.74 (d, *J* = 8.4 Hz, 2H), 2.90 (dd, *J* = 16.4 Hz, 6.4 Hz, 2H), 2.63 (dd, *J*= 16.8 Hz, 7.2 Hz, 2H), 2.31-2.26 (m, 8H), 1.82-1.77 (m, 2H), 1.60-1.49 (m, 4H) ppm.

Example 12

[0152] Compound **3g-Bn** prepared in example 6 was used as a hydrogenation substrate and compound Ir(I)/(*S,S*)-**7c** was used as a catalyst to prepare chiral aromatic spiroketal compound (*R,R,R*)-**5g**. The reaction was conducted as follows: **3g-Bn** (273 mg, 0.5mmol), catalyst Ir(I)/(*S,S*)-**7c** (4.8mg, 0.003mmol) and 10 mL of anhydrous dichloromethane were added to a hydrogenation flask. The hydrogenation flask was placed in a glovebox and transferred to a high pressure reactor. Hydrogen displacement was performed for three times, and then the reactor was charged with 50 atm of hydrogen. The reaction was carried out at room temperature for 6 hrs. After hydrogen was discharged, the reactor was opened and 20 mg of Pd/C was directly added to the hydrogenation flask which was then placed in a reactor. The reactor was charged with 5 atm of hydrogen and the reaction was carried out for 10 hrs. After hydrogen was discharged,

the reaction mixture was filtered and concentrated and the residue was separated by column chromatography to obtain (*R,R,R*)-**5g** in 79% yield, the ee value of which was more than 99%.

[0153] *(R,R,R)-5g,* $[\alpha]_D^{20}$ = -71.3 *(c* 1.05, $CHCl_3$), >99% ee (determined by high performance liquid chromatography, chiral AD-H column; n-hexane/isobutanol = 95 : 5, 1.0 mL/min, 230 nm; t_R (major) = 5.78 min; t_R (minor) = 6.26 min). ^1H NMR (400 MHz, $CDCl_3$) δ 7.35-7.20 (m, 2H), 7.05-6.99 (m, 2H), 6.58-6.46 (m, 2H), 3.78 (s, 6H), 2.99-2.87 (m, 2H), 2.73-2.60 (m, 2H), 2.38-2.30 (m, 2H),1.91-1.78 (m, 2H), 1.70-1.51(m, 4H) ppm.

Example 13

[0154] Compound **3h-Bn** prepared in example 6 was used as a hydrogenation substrate and compound Ir(I)/(*S,S*)-**7a** was used as a catalyst to prepare chiral aromatic spiroketal compound (*R,R,R*)-**5h**. The reaction was conducted as follows: **3h-Bn** (262 mg, 0.5 mmol), catalyst Ir(I)/(*S,S*)-**7a** (4.8 mg, 0.003 mmol) and 10 mL of anhydrous dichloromethane were added to a hydrogenation flask. The hydrogenation flask was placed in a glovebox and transferred to a high pressure reactor. Hydrogen displacement was performed for three times, and then the reactor was charged with 50 atm of hydrogen. The reaction was carried out at room temperature for 6 hrs. After hydrogen was discharged, the reactor was opened and 20 mg of Pd/C was directly added to the hydrogenation flask which was then placed in a reactor. The reactor was charged with 5 atm of hydrogen and the reaction was carried out for 10 hrs. After hydrogen was discharged, the reaction mixture was filtered and concentrated and the residue was separated by column chromatography to obtain (*R,R,R*)-**5h** in 70% yield, the ee value of which was more than 96%.

[0155] (*S,S,R*)-**5h**, $[\alpha]_D^{20}$ = -29.1 (*c* 0.95, $CHCl_3$), 96% *ee* (determined by high performance liquid chromatography, chiral AD-H column; n-hexane/isobutanol = 98:2, 1.0 mL/min, 254 nm; t_R (major) = 15.32 min; t_R (minor) = 18.07 min). ^1H NMR (400 MHz, $CDCl_3$) δ 7.25-7.12 (m, 2H), 6.96-6.89 (m, 4H), 3.95 (dd, *J* = 16.6, 4.2 Hz, 2H), 3.65 (dd, *J* = 15.2, 5.8 Hz, 2H), 3.04 (dd, *J* = 16.9, 6.4 Hz, 2H), 2.81-2.75 (m, 2H), 2.42-2.32 (m, 2H) ppm; ^{19}F NMR (282 MHz, $CDCl_3$) δ 111.5 ppm.

Example 14

[0156] Compound **3i-Bn** prepared in example 6 was used as a hydrogenation substrate and compound Ir(I)/(*S,S*)-**7c** was used as a catalyst to prepare chiral aromatic spiroketal compound (*R,R,R*)-**5i**. The reaction was conducted as follows: **3i-Bn** (268 mg, 0.5mmol), catalyst Ir(I)/(*S,S*)-**7c** (4.8mg, 0.003mmol) and 10 mL of anhydrous dichloromethane were added to a hydrogenation flask. The hydrogenation flask was placed in a glovebox and transferred to a high pressure reactor. Hydrogen displacement was performed for three times, and then the reactor was charged with 50 atm of hydrogen. The reaction was carried out at room temperature for 6 hrs. After hydrogen was discharged, the reactor was opened and 20 mg of Pd/C was directly added to the hydrogenation flask which was then placed in a reactor. The reactor was charged with 5 atm of hydrogen and the reaction was carried out for 10 hrs. After hydrogen was discharged, the reaction mixture was filtered and concentrated and the residue was separated by column chromatography to obtain (*R,R,R*)-**5i** in 75% yield, the ee value of which was more than 99%.

[0157] (*R,R,R*)-**5i**, $[\alpha]_D^{20}$ = -55.1 *(c* 1.00, $CHCl_3$), >99% ee (determined by high performance liquid chromatography, chiral AD-H column; n-hexane/isobutanol = 95 : 5, 1.0 mL/min, 230 nm; t_R (minor) = 5.82 min; t_R (major) = 7.23 min). ^1H NMR (400 MHz, $CDCl_3$) δ 7.08 (d, *J* = 12.4 Hz, 2H), 6.92 (t, *J* = 7.4 Hz, 2H), 6.88-6.82 (m, 2H), 2.64 (dd, *J* = 16.2, 4.2 Hz, 2H), 2.34-2.25 (m, 2H), 1.98-1.97 (m, 2H), 1.75-1.72 (m, 4H), 1.63-1.45 (m, 4H) ppm; ^{19}F NMR (282 MHz, $CDCl_3$) δ 115.8 ppm.

Example 15

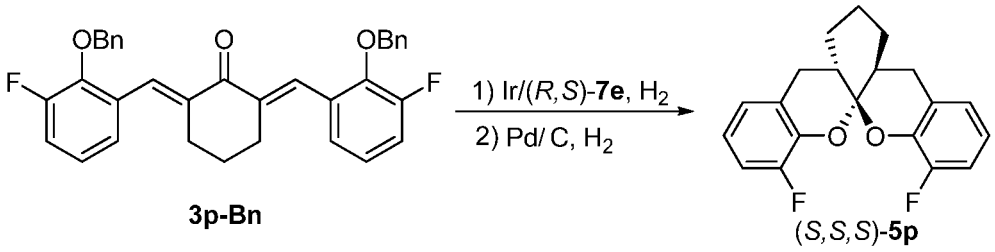
[0158] Compound **3j-Bn** prepared in example 6 was used as a hydrogenation substrate and compound Ir(I)/(*S,S*)-**7c** was used as a catalyst to prepare chiral aromatic spiroketal compound (*R,R,R*)-**5j**. The reaction was conducted as follows: **3j-Bn** (268 mg, 0.5mmol), catalyst Ir(I)/(*S,S*)-**7c** (4.8mg, 0.003mmol) and 10 mL of anhydrous dichloromethane were added to a hydrogenation flask. The hydrogenation flask was placed in a glovebox and transferred to a high pressure reactor. Hydrogen displacement was performed for three times, and then the reactor was charged with 50 atm of hydrogen. The reaction was carried out at room temperature for 6 hrs. After hydrogen was discharged, the reactor was opened and 20 mg of Pd/C was directly added to the hydrogenation flask which was then placed in a reactor. The reactor was charged with 5 atm of hydrogen and the reaction was carried out for 10 hrs. After hydrogen was discharged, the reaction mixture was filtered and concentrated and the residue was separated by column chromatography to obtain *(R,R,R)*-**5j** in 60% yield, the ee value of which was more than 99%.

[0159] *(R,R,R)*-**5j,** $[\alpha]_D^{20}$ = +99.2 *(c* 1.00, $CHCl_3$), >99% *ee* (determined by high performance liquid chromatography, chiral AD-H column; n-hexane/isobutanol = 95:5, 1.0 mL/min, 230 nm; t_R (major) = 11.13 min; t_R (minor) = 12.90 min). ^1H NMR (400 MHz, $CDCl_3$) δ 7.14-7.09 (m, 4H), 6.98-6.83 (m, 2H), 2.76 (dd, *J* = 14.8, 4.2 Hz, 2H), 2.34-2.28 (m, 2H),

1.26-1.93 (m, 2H), 1.79-1.72 (m, 2H), 1.58-1.48 (m, 2H) ppm; ^{19}F NMR (282 MHz, $CDCl_3$) δ 127.9 ppm.

Example 16

[0160] Compound *(S,S,S)*-**5p** was prepared according to the preparation method of example 5.

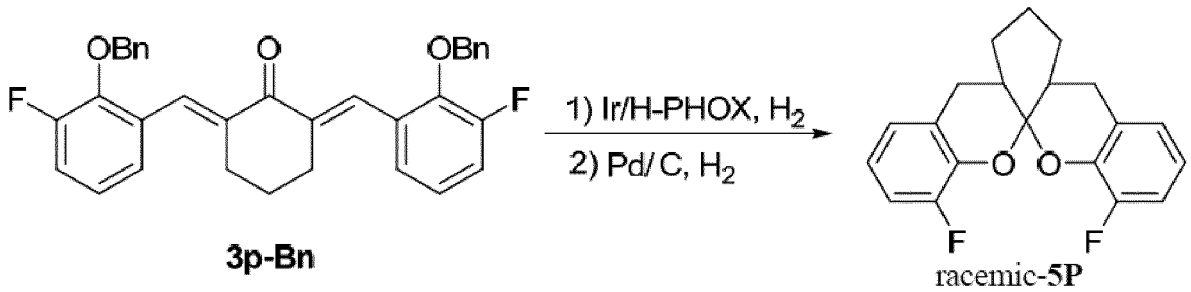


3p-Bn (*S,S,S*)-**5p**

[0161] Compound **3p-Bn** was used as a hydrogenation substrate and Ir(I)/(*R,S*)-**7e** was used as a catalyst. The reaction was conducted as follows: **3p-Bn** (52 mg, 0.1mmol), Ir(I)/(*S,S*)-**7c** (7.4mg, 0.005mmol) and 2 mL of anhydrous dichloromethane were added to a hydrogenation flask. The hydrogenation flask was placed in a glovebox and transferred to a high pressure reactor. Hydrogen displacement was performed for three times, the reactor was charged with 50 atm of hydrogen. The reaction was carried out at room temperature for 6 hrs. After hydrogen was discharged, the reactor was opened and 10 mg of Pd/C was directly added to the hydrogenation flask which was then placed in a reactor. The reactor was charged with 5 atm of hydrogen and the reaction was carried out for 10 hrs. After hydrogen was discharged, the reaction mixture was filtered and concentrated and the residue was separated by column chromatography. The yield of the obtained trans-**5P** was 91% yield, the mole raio of trans-form and cis-form was 92/8, and the ee value of trans-**5P** was more than 99%. The NMR data was the same as that of compound 5P prepared in example 3. The absolute configuration was *(S,S,S)*.

Example 17

[0162] Racemic compound **5p** was prepared according to the preparation method of example 5.

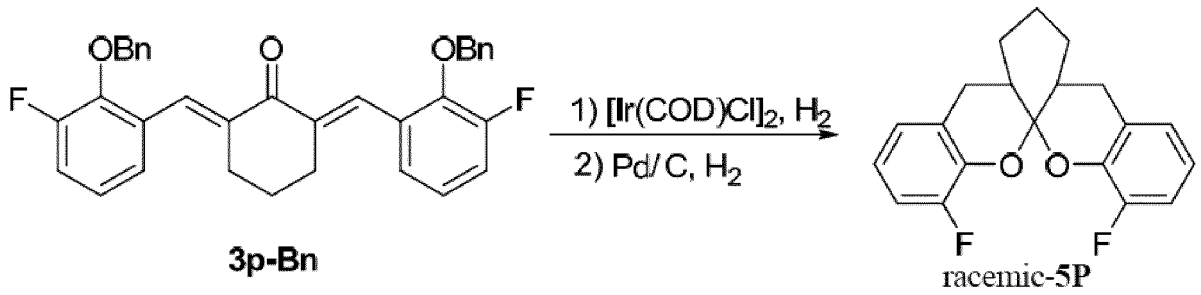


3p-Bn racemic-**5P**

[0163] Compound **3p-Bn** was used as a hydrogenation substrate and Ir(I)/H-PHOX was used as a catalyst. The reaction was conducted as follows: **3p-Bn** (52 mg, 0.1mmol), Ir(I)/H-PHOX (1.6mg, 0.001mmol) and 2 mL of anhydrous dichloromethane were added to a hydrogenation flask. The hydrogenation flask was placed in a glovebox and transferred to a high pressure reactor. Hydrogen displacement was performed for three times, and then the reactor was charged with 50 atm of hydrogen. The reaction was carried out at room temperature for 6 hrs. After hydrogen was discharged, the reactor was opened and 10 mg of Pd/C was directly added to the hydrogenation flask which was then placed in a reactor. The reactor was charged with 5 atm of hydrogen and the reaction was carried out for 10 hrs. After hydrogen was discharged, the reaction mixture was filtered and concentrated and the residue was separated by column chromatography to obtain racemic trans-**5p** in 45% yield.

Example 18

[0164] Racemic compound **5p** was prepared according to the preparation method of example 5.



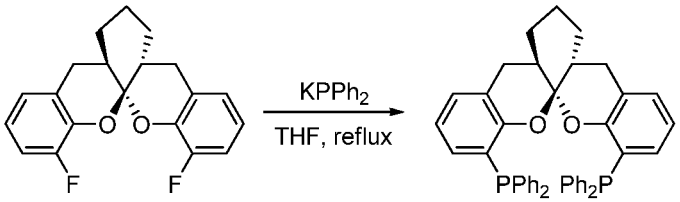
3p-Bn

racemic-5P

[0165] Compound **3p-Bn** was used as a hydrogenation substrate and $[Ir(COD)Cl]_2$ was used as a catalyst. The reaction was conducted as follows: **3p-Bn** (52 mg, 0.1 mmol), $[Ir(COD)Cl]_2$ (3.3 mg, 0.005 mmol) and 2 mL of anhydrous dichloromethane were added to a hydrogenation flask. The hydrogenation flask was placed in a glovebox and transferred to a high pressure reactor. Hydrogen displacement was performed for three times, and then the reactor was charged with 50 atm of hydrogen. The reaction was carried out at room temperature for 6 hrs. After hydrogen was discharged, the reactor was opened and 10 mg of Pd/C was directly added to the hydrogenation flask which was then placed in a reactor. The reactor was charged with 5 atm of hydrogen and the reaction was carried out for 10 hrs. After hydrogen was discharged, the reaction mixture was filtered and concentrated and the residue was separated by column chromatography to obtain racemic trans-**5p** in 40% yield.

Example 19

[0166]



(*R,R,R*)-**5p** (*R,R,R*)-**6a**

[0167] (*R*,*R*,*R*)-**5p** (500 mg, 1.52 mmol), anhydrous tetrahydrofuran (4 mL) and potassium diphenyl phosphine ($KPPh_2$, 9.12 mL, 0.5 mol/L in THF, 4.56 mmol) were added to a 50 mL of water-free and oxygen-free Schlenk tube and heated to reflux for 5 hr. After cooled, 10 mL of distilled water was added to quench the reaction. The reaction mixture was extracted with dichloromethane (3×10 mL) and the organic phase was dried on anhydrous sodium sulfate. After filtered and concentrated, the residue was purified by column chromatography to obtain target product *(R,R,R)*-**6a** in 80% yield.

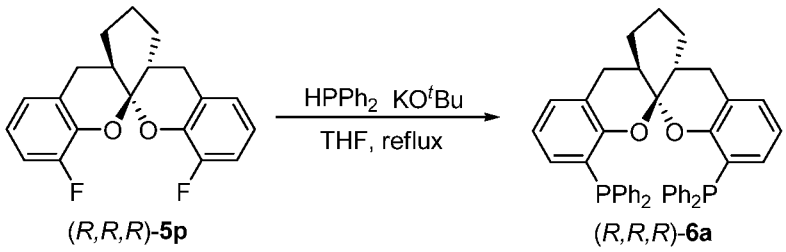
[0168] *(R,R,R)*-**6a**, white solid. Mp 101-103 °C, $[\alpha]_D^{20}$ = +113.4 (c 1.00, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 7.30-7.26 (m, 20H), 6.89 (d, *J* = 7.2 Hz, 2H), 6.74 (t, *J* = 7.2 Hz, 2H), 6.53-6.50 (m, 2H), 2.34-2.30 (m, 4H), 1.95-1.92 (m, 2H), 1.30-1.29 (m, 2H), 1.17-1.15 (m, 4H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.1 (d, $J_{(P,C)}$ = 14.2 Hz), 137.1 (d, $J_{(P,C)}$ = 11.8 Hz), 136.7 (d, $J_{(P,C)}$ = 10.9 Hz), 134.2 (d, $J_{(P,C)}$ = 21.9 Hz), 133.9 (d, $J_{(P,C)}$ = 20.2 Hz), 130.9 (d, $J_{(P,C)}$ = 3.2 Hz), 129.9 (s), 128.5 (s), 128.2-128.1 (m), 124.9 (d, $J_{(P,C)}$ = 14.1 Hz), 120.4-120.3 (m), 101.3, 33.5, 27.6, 26.7, 19.4 ppm; ^{31}P(162 MHz,$CDCl_3$) δ -15.8 (s) ppm.

Example 20

[0169] (*R*,*R*,*R*)-**5p** (500 mg, 1.52 mmol), anhydrous tetrahydrofuran (4 mL) and lithium diphenyl phosphine ($LiPPh_2$, 9.12 mL, 0.5 mol/L in THF, 4.56 mmol) were added to a 50 mL of water-free and oxygen-free Schlenk tube and heated to reflux for 6 hr. After cooled, 10 mL of distilled water was added to quench the reaction. The reaction mixture was extracted with dichloromethane (3×10 mL) and the organic phase was dried on anhydrous sodium sulfate. After filtered and concentrated, the residue was purified by column chromatography to obtain pure bisphosphine ligand *(R,R,R)*-**6a** in 75% yield.

Example 21

[0170]

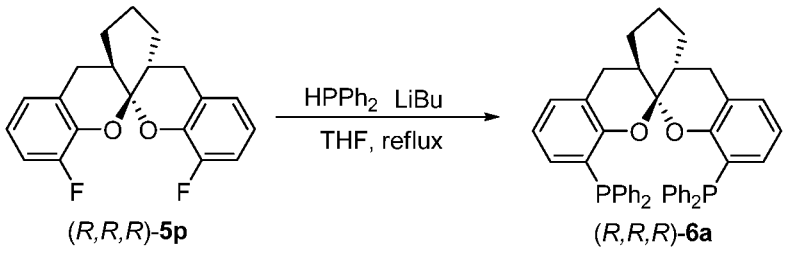


(*R,R,R*)-**5p** (*R,R,R*)-**6a**

[0171] (*R,R,R*)**-5p** (500 mg, 1.52 mmol), anhydrous tetrahydrofuran (10 mL), diphenyl phosphine (849 mg, 4.56 mmol) and potassium tert-butoxide (511.6 mg, 4.56 mmol) were added to a 50 mL of water-free and oxygen-free Schlenk tube and heated to reflux for 10 hr. After cooled, 10 mL of distilled water was added to quench the reaction. The reaction mixture was extracted with dichloromethane (3 × 10 mL) and the organic phase was dried on anhydrous sodium sulfate. After filtered and concentrated, the residue was purified by column chromatography to obtain pure bisphosphine ligand *(R,R,R)*-**6a** in 77% yield.

Example 22

[0172]

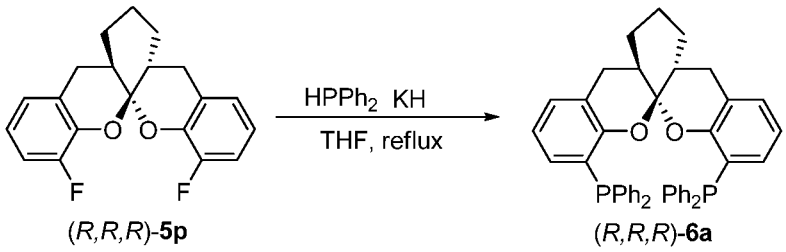


(*R,R,R*)-**5p** (*R,R,R*)-**6a**

[0173] Diphenyl phosphine (849 mg, 4.56 mmol) and anhydrous tetrahydrofuran (10 mL) were added to a 50 mL of water-free and oxygen-free Schlenk tube and cooled to below -78 °C. n-butyllithium (2.85 mL, 1.6 mol/L, 4.56 mmol) was slowly added dropwise, stirred at below -78 °C for 0.5 hr and then warmed to room temperature. (*R,R,R*)**-5p** (500 mg, 1.52 mmol) was added and heated to reflux for 12 hrs and then cooled to room temperature. The reaction mixture was concentrated and directly purified by column chromatography to obtain *(R,R,R)*-**6a** as white solids in 76% yield.

Example 23

[0174]

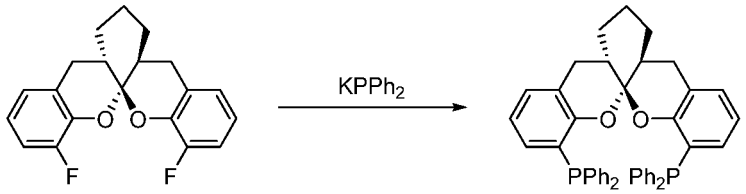


(*R,R,R*)-**5p** (*R,R,R*)-**6a**

[0175] Diphenyl phosphine (849 mg, 4.56 mmol), potassium hydride (182.4 mg, 4.56 mmol) and anhydrous tetrahydrofuran (10 mL) were added to a 50 mL of water-free and oxygen-free Schlenk tube at room temperature and stirred for 0.5 hr. *(R,R,R)*-**5p** (500 mg, 1.52 mmol) was added and heated to reflux for 12 hrs and then cooled to room temperature. The reaction mixture was concentrated and directly purified by column chromatography to obtain *(R,R,R)*-**6a** as white solids in 89% yield.

Example 24

[0176] The reaction route for preparing *(S,S,S)-6a* was shown as follows.

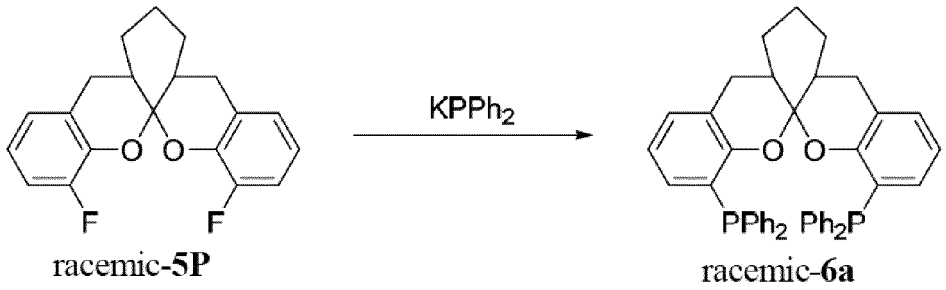


(*S,S,S*)-**5p** (*S,S,S*)-**6a**

[0177] *(S,S,S)*-**5g** (328 mg, 1.0 mmol), anhydrous tetrahydrofuran (4 mL) and potassium diphenyl phosphine ($KPPh_2$, 6.0 mL, 0.5 mol/L in THF, 3.0 mmol) were added to a 50 mL of water-free and oxygen-free Schlenk tube and heated to reflux for 10 hrs. After cooled, 10 mL of distilled water was added to quench the reaction and the reaction mixture was extracted with dichloromethane (3×10 mL). The organic phase was dried on anhydrous sodium sulfate, filtered and concentrated. The residue was purified by column chromatography to obtain target product, *(S,S,S)*-**6a** in 74% yield.

Example 25

[0178] The reaction route for preparing racemic **6a** was shown as follows.

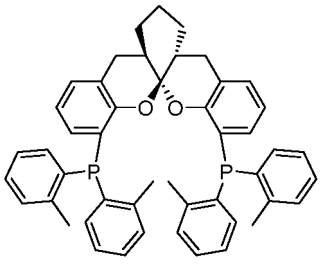


racemic-**5P** racemic-**6a**

[0179] Racemic compound **5p** (500 mg, 1.52 mmol), anhydrous tetrahydrofuran (4 mL) and potassium diphenyl phosphine ($KPPh_2$, 9.12 mL, 0.5 mol/L in THF, 4.56 mmol) were added to a 50 mL of water-free and oxygen-free Schlenk tube and heated to reflux for 5 hrs. After cooled, 10 mL of distilled water was added to quench the reaction and the reaction mixture was extracted with dichloromethane (3 × 10 mL). The organic phase was dried on anhydrous sodium sulfate, filtered and concentrated. The residue was purified by column chromatography to obtain target product, racemic **6a** in 80% yield.

Example 26

[0180] The preparation method in this example was the same as that of example 23 except that diphenyl phosphine was replaced by di(o-tolyl)phosphine to prepare chiral aromatic spiroketal bisphosphine ligand (*R,R,R*)-**6b.**

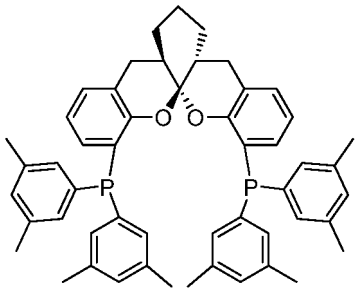


[0181] *(R,R,R)*- **6b,** white solid, 40% yield. Mp 125-127 °C, $[\alpha]_D^{20}$ = +143.5 (c 1.00, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ = 7.24-7.12 (m, 8H), 7.05 (t, *J* = 7.2 Hz, 4H), 6.88-6.85 (m, 4H), 6.79-6.72 (m, 4H), 6.53-6.50 (m, 2H), 2.39 (s, 6H), 2.34-2.23 (m, 2H), 2.18 (s, 6H), 1.99-1.95 (m, 2H), 1.34-1.15 (m, 8H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.5 (d, $J_{(P,C)}$ = 15.2 Hz), 143.2 (d, $J_{(P,C)}$ = 28.3 Hz), 142.7 (d, $J_{(P,C)}$ = 25.9 Hz), 135.3 (d, $J_{(P,C)}$ = 11.4 Hz), 134.9 (d, $J_{(P,C)}$ = 13.8 Hz), 133.5 (d, $J_{(P,C)}$ = 40.1 Hz), 131.0 (d, $J_{(P,C)}$ = 2.9 Hz), 130.0-129.6 (m), 128.3 (d, $J_{(P,C)}$ = 15.8 Hz), 125.8 (d, $J_{(P,C)}$ = 24.0 Hz), 123.3 (d, $J_{(P,C)}$ = 12.7 Hz), 120.6-120.5 (m), 101.4, 33.3, 27.7, 26.6, 21.2 (d, $J_{(P,C)}$ = 21.1 Hz), 21.0 (d, $J_{(P,C)}$ = 23.7

Hz), 19.3 ppm; ^{31}P(121 MHz,$CDCl_3$) δ -33.4 ppm.

Example 27

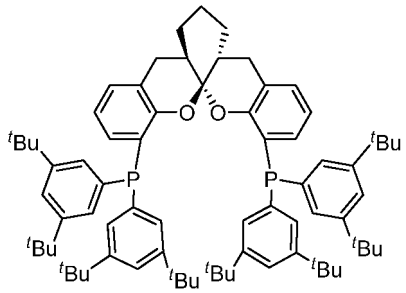
[0182] The preparation method in this example was the same as that of example 23 except that diphenyl phosphine was replaced by di(3,5-dimethylphenyl)phosphine to prepare chiral aromatic spiroketal bisphosphine ligand *(R,R,R)*-**6c**.



[0183] *(R,R,R)*-**6c**, white solid, 70% yield. Mp 102-103 °C, $[\alpha]_D^{20}$ = +166.5 *(c* 1.00, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 6.93-6.84 (m, 14H), 6.73 (t, *J* = 6.9 Hz, 2H), 6.47 (t, *J* = 4.8 Hz, 2H), 2.45-2.38 (m, 4H), 2.24 (s, 12H), 2.21 (s, 12H), 2.04-1.97 (m, 2H), 1.30-1.26 (m, 2H), 1.12-1.07 (m, 4H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 153.1 (d, $J_{(P,C)}$ = 14.7 Hz), 137.3 (d, $J_{(P,C)}$ = 7.4 Hz), 137.2 (d, $J_{(P,C)}$ = 7.8 Hz), 136.9 (d, $J_{(P,C)}$ = 10.2 Hz), 136.5 (d, $J_{(P,C)}$ = 10.9 Hz), 132.1 (s), 131.8 (s), 131.5 (s), 130.8 (d, $J_{(P,C)}$ = 1.5 Hz), 130.2 (s), 129.8 (d, $J_{(P,C)}$ = 41.7 Hz), 125.5 (d, $J_{(P,C)}$ = 14.2 Hz), 120.1 (s), 120.1 (d, $J_{(P,C)}$ = 1.7 Hz), 101.1, 33.4, 27.3, 26.7, 21.3, 21.2, 19.5 ppm; ^{31}P(121 MHz,$CDCl_3$) δ -15.2 ppm.

Example 28

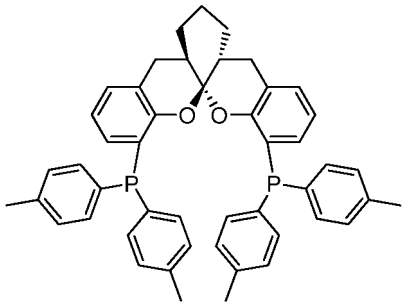
[0184] The preparation method in this example was the same as that of example 23 except that diphenyl phosphine was replaced by bis(3,5-di-tert-butylphenyl)phosphine to prepare chiral aromatic spiroketal bisphosphine ligand *(R,R,R)*-**6d**.



[0185] *(R,R,R)*-**6d**, white solid, 45% yield. Mp 100-101 °C, $[\alpha]_D^{20}$ = +140.5 *(c* 1.00, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.91-6.82 (m, 14H), 6.69 (t, *J* = 6.6 Hz, 2H), 6.37 (t, *J* = 5.0 Hz, 2H), 2.41-2.32 (m, 4H), 2.28 (s, 36H), 2.15 (s, 36H), 2.10-1.97 (m, 2H), 1.30-1.28 (m, 2H), 1.11-1.09 (m, 4H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 155.1 (d, $J_{(P,C)}$ = 15.0 Hz), 139.5 (d, $J_{(P,C)}$ = 8.4 Hz), 137.7 (d, $J_{(P,C)}$ = 8.0 Hz), 136.1 (d, $J_{(P,C)}$ = 10.8 Hz), 135.4 (d, $J_{(P,C)}$ = 11.2 Hz), 133.4 (s), 131.8 (s), 130.9 (s), 130.8 (d, $J_{(P,C)}$ = 12.0 Hz), 130.4 (s), 129.6 (d, $J_{(P,C)}$ = 42.2 Hz), 126.5 (d, $J_{(P,C)}$ = 16.2 Hz), 120.9 (s), 120.4 (d, $J_{(P,C)}$ = 2.2 Hz), 99.1, 33.4, 29.8, 27.3, 26.7, 25.6, 21.3, 21.2, 19.5 ppm; ^{31}P(121 MHz,$CDCl_3$) δ -17.8 ppm.

Example 29

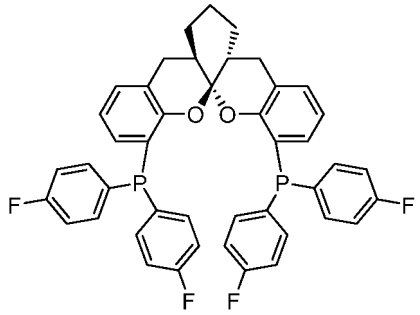
[0186] The preparation method in this example was the same as that of example 23 except that diphenyl phosphine was replaced by di(*p*-tolyl)phosphine to prepare chiral aromatic spiroketal bisphosphine ligand (*R*,*R*,*R*)-**6e**.



[0187] *(R,R,R)*-**6e**, white solid, 67% yield. Mp 90-92 °C, $[\alpha]_D^{20}$ = +118.5 (*c* 1.00, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ = 7.21-7.14 (m, 8H), 7.10-7.07 (m, 8H), 6.87 (d, *J* = 7.2 Hz, 2H), 6.73 (t, *J* = 7.6 Hz, 2H), 6.54 (t, *J* = 5.6 Hz, 2H), 2.36-2.25 (m, 16H), 1.96-1.92 (m, 2H), 1.32-1.26 (m, 2H), 1.19-1.15 (m, 4H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 153.1 (d, $J_{(P,C)}$ = 14.5 Hz), 138.2 (s), 137.8 (s), 134.3-133.8 (m), 133.4 (d, $J_{(P,C)}$ = 10.4 Hz), 130.8 (d, $J_{(P,C)}$ = 2.6 Hz), 129.7 (s), 129.0-128.9 (m), 125.5 (d, $J_{(P,C)}$ = 14.0 Hz), 120.3-120.2 (m), 101.2, 33.4, 27.6, 26.7, 21.3, 19.4 ppm; ^{31}P NMR (162 MHz,$CDCl_3$) δ -17.9 ppm.

Example 30

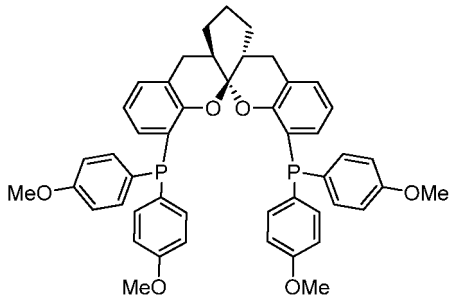
[0188] The preparation method in this example was the same as that of example 23 except that diphenyl phosphine was replaced by di(*p*-fluorophenyl)phosphine to prepare chiral aromatic spiroketal bisphosphine ligand (*R*,*R*,*R*)-**6f**.



[0189] *(R,R,R)*-**6f**, white solid, 80% yield. Mp 76-77 °C, $[\alpha]_D^{20}$ = +88.0 (c 1.00, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ = 7.27-7.20 (m, 8H), 6.99-6.93 (m, 10H), 6.76 (t, *J* = 7.6 Hz, 2H), 6.49-6.46 (m, 2H), 2.50-2.39 (m, 4H), 2.01-1.94 (m, 2H), 1.33-1.32 (m, 2H), 1.20-1.11 (m, 4H) ppm; ^{31}P NMR (162 MHz,$CDCl_3$) δ -17.8 ppm; ^{19}F NMR (376 MHz,$CDCl_3$) δ -112.3, -112.5 ppm.

Example 31

[0190] The preparation method in this example was the same as that of example 23 except that diphenyl phosphine was replaced by di(*p*-methoxyphenyl)phosphine to prepare chiral aromatic spiroketal bisphosphine ligand (R,R,R)-**6g**.

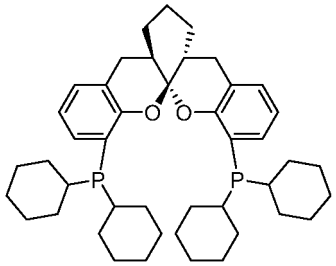


[0191] *(R,R,R)*-**6g**, white solid, 65% yield. Mp 91-92 °C, $[\alpha]_D^{20}$ = +122.5 *(c* 1.00, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ = 7.26-7.19 (m, 8H), 6.88-6.87 (m, 2H), 6.84-6.81 (m, 8H), 6.73 (t, *J* = 7.2 Hz, 2H), 6.51 (t, *J* = 5.2 Hz, 2H), 3.75 (s,

6H), 3.71 (s, 6H), 2.35-2.31 (m, 4H), 1.94-1.91 (m, 2H), 1.31-1.26 (m, 3H), 1.20-1.16 (m, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 159.8 (d, $J_{(P,C)}$ = 38.8 Hz), 152.8 (d, $J_{(P,C)}$ = 13.9 Hz), 135.5-135.0 (m), 130.4 (s), 129.5 (s), 128.3 (d, $J_{(P,C)}$ = 8.1 Hz), 127.6 (d, $J_{(P,C)}$ = 9.0 Hz), 125.8 (d, $J_{(P,C)}$ = 13.3 Hz), 120.1 (d, $J_{(P,C)}$ = 1.6 Hz), 113.8-113.7 (m), 101.0, 55.0, 54.9, 33.4, 27.6, 26.6, 19.3 ppm; ^{31}P NMR (162 MHz,$CDCl_3$) δ -18.8 ppm.

Example 32

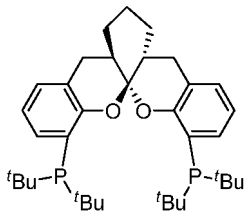
[0192] The preparation method in this example was the same as that of example 23 except that diphenyl phosphine was replaced by dicyclohexylphosphine to prepare chiral aromatic spiroketal bisphosphine ligand *(R,R,R)*-**6h**.



[0193] *(R,R,R)-6h,* white solid, 55% yield. Mp 95-96 °C, $[\alpha]_D^{20}$ = +88.5 *(c* 1.00, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ = 7.21-7.15 (m, 4H), 6.89-6.85(m, 2H), 2.39-2.30 (m, 8H), 1.98-1.87 (m, 6H), 1.30-1.25 (m, 18H), 1.23-1.14 (m, 20 H) ppm; ^{31}P NMR (162 MHz,$CDCl_3$) δ -21.6 ppm.

Example 33

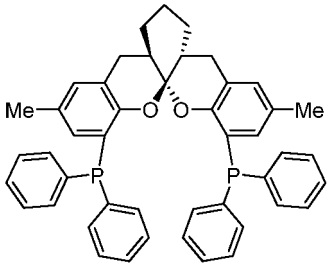
[0194] The preparation method in this example was the same as that of example 23 except that diphenyl phosphine was replaced by di-tert-butylphosphine to prepare chiral aromatic spiroketal bisphosphine ligand *(R,R,R)*-**6i**.



[0195] *(R,R,R)-6i,* white solid, 81% yield. $[\alpha]_D^{20}$ = +78.1 *(c* 1.00, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ = 7.28-7.21 (m, 2H), 6.99-6.81(m, 4H), 2.38-2.21 (m, 4H), 1.98-1.88 (m, 6H), 1.66-1.45 (m, 14H), 1.30-1.29 (m, 8H), 1.17-1.15 (m, 16H) ppm; ^{31}P NMR (162 MHz,$CDCl_3$) δ -22.8 ppm.

Example 34

[0196] The preparation method in this example was the same as that of example 19 except that *(R,R,R)*-**5b** was used as raw material to prepare chiral aromatic spiroketal bisphosphine ligand *(R,R,R)*-**6j**.

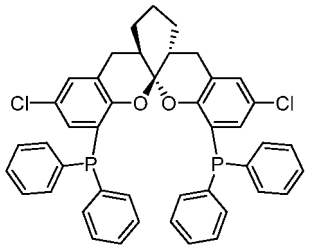


[0197] *(R,R,R)*-**6j**, white solid, 70% yield. Mp 98-100 °C, $[\alpha]_D^{20}$ = +109.3 (c 1.00, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 7.31-7.24 (m, 20H), 6.69 (s, 2H), 6.35 (d, *J* = 5.6 Hz, 2H), 2.31-2.26 (m, 4H), 2.11 (s, 6H), 1.92-1.86 (m, 2H), 1.28-1.25

(m, 2H), 1.16-1.13 (m, 4H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.2, 151.1, 137.3, 137.2, 137.0, 136.9, 134.3, 134.1, 133.9, 133.7, 131.5, 131.4, 130.6, 129.2, 128.9, 128.4, 128.1, 128.0, 125.2, 124.4, 124.3, 120.1, 101.2, 33.4, 27.7, 26.7, 20.6, 19.4 ppm; ^{31}P(162 MHz,$CDCl_3$) δ -15.3 ppm.

Example 35

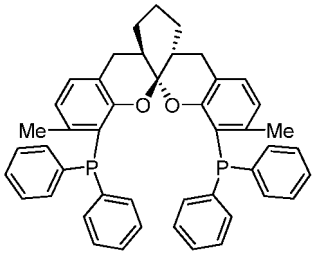
[0198] The preparation method in this example was the same as that of example 19 except that *(R,R,R)*-**5c** was used as raw material to prepare chiral aromatic spiroketal bisphosphine ligand (*R,R,R*)-**6k**.



[0199] *(R,R,R)*-**6k**, white solid, 65% yield. Mp 98-100 °C, $[\alpha]_D^{20}$ = +101.1 *(c* 1.00, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33-7.24 (m, 20H), 6.85 (s, 2H), 6.46-6.44 (m, 2H), 2.34-2.19 (m, 4H), 1.91-1.85 (m, 2H), 1.28-1.26 (m, 2H), 1.14-1.11 (m, 4H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.4, 151.3, 136.2, 136.1, 135.6, 135.5, 134.2, 134.05, 134.02, 133.8, 130.2, 130.1, 129.4, 128.9, 128.6, 128.46, 128.42, 128.38, 128.34, 127.7, 127.5, 125.5, 122.02, 122.01, 101.6, 33.2, 27.5, 26.6, 19.2 ppm; ^{31}P(162 MHz,$CDCl_3$) δ -15.5 ppm.

Example 36

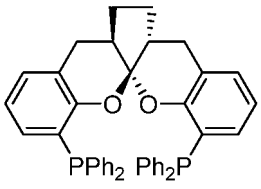
[0200] The preparation method in this example was the same as that of example 19 except that (*R,R,R*)-**5d** was used as raw material to prepare chiral aromatic spiroketal bisphosphine ligand (*R,R,R*)-**6l.**



[0201] *(R,R,R)*-**6l**, white solid, 47% yield. Mp 110-112 °C, $[\alpha]_D^{20}$ = +100.3 (c 0.90, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31-7.24 (m, 20H), 6.88-6.79 (m, 2H), 6.56-6.37 (m, 2H), 2.36-2.29 (m, 4H), 2.18 (s, 6H), 1.94-1.83 (m, 2H), 1.29-1.21 (m, 2H), 1.17-1.12 (m, 4H) ppm; ^{31}P(162 MHz,$CDCl_3$) δ -14.6 ppm.

Example 37

[0202] The preparation method in this example was the same as that of example 19 except that (*R,R,R*)-**5h** was used as raw material to prepare chiral aromatic spiroketal bisphosphine ligand (*R,R,R*)-**6m.**

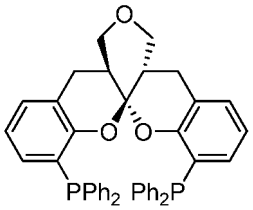


[0203] *(R,R,R)*-**6m,** white solid, 75% yield. Mp 109-111 °C, $[\alpha]_D^{20}$ = +83.1 *(c* 1.00, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42-7.17 (m, 20H), 6.95 (d, *J* = 7.2 Hz, 2H), 6.76 (t, *J* = 7.6 Hz, 2H), 6.58 (t, *J* = 7.2 Hz, 2H), 2.45 (dd, *J* = 16.0 Hz, 6.4 Hz, 2H), 2.28 (dd, *J* = 16.0 Hz, 6.8 Hz, 2H), 1.98-1.95 (m, 2H), 1.47-1.43 (m, 2H), 1.12-1.08 (m, 2H) ppm; ^{31}P(162

MHz,$CDCl_3$) δ -15.5 ppm.

Example 38

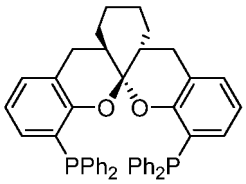
[0204] The preparation method in this example was the same as that of example 19 except that *(S,S,R)*-**5i** was used as raw material to prepare chiral aromatic spiroketal bisphosphine ligand *(S,S,R)*-**6n**.



[0205] *(S,S,R)-6n,* white solid, 79% yield. Mp 111-112 °C, $[\alpha]_D^{20}$ = +75.2 *(c* 1.10, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 7.45-7.16 (m, 20H), 6.99-6.81 (m, 4H), 6.63-6.58 (m, 2H), 3.34-3.31 (m, 4H), 2.48-2.44 (m, 2H), 2.32-2.29 (m, 2H), 1.48-1.41 (m, 2H) ppm; ^{31}P(162 MHz,$CDCl_3$) δ -17.3 ppm.

Example 39

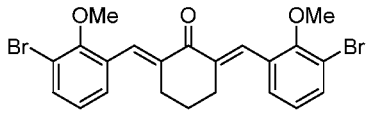
[0206] The preparation method in this example was the same as that of example 19 except that (*R,R,R*)-**5j** was used as raw material to prepare chiral aromatic spiroketal bisphosphine ligand (*R,R,R*)-**6o.**



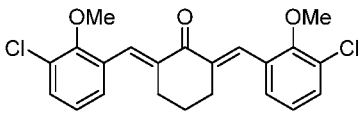
[0207] (*R,R,R*)-**6o,** white solid, 81% yield. Mp 89-92 °C, $[\alpha]_D^{20}$ = +112.2 (c 1.30, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 7.35-7.14 (m, 20H), 6.91-6.85 (m, 2H), 6.76-6.58 (m, 4H), 2.46-2.41 (m, 2H), 2.34-2.31 (m, 2H), 1.48-1.41 (m, 6H), 1.22-1.09 (m, 4H) ppm; ^{31}P(162 MHz,$CDCl_3$) δ -13.4 ppm.

Example 40

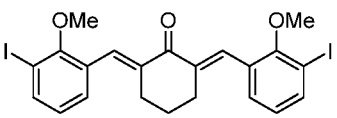
[0208] Compounds of formulae **3k-Me - 3m-Me** were prepared according to the preparation method of example 2, respectively.



3k-Me



3l-Me

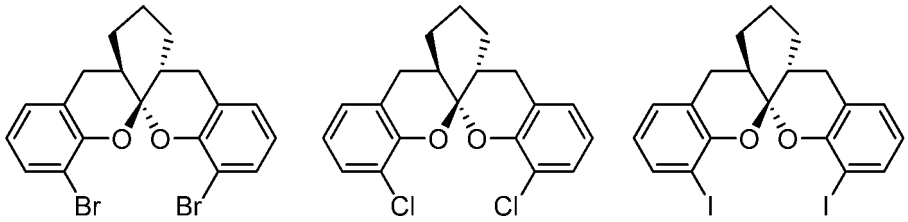


3m-Me

[0209] 3k-Me, ESI-MS m/z: 490.9 [M+H^+]; 31-Me, ESI-MS m/z: 403.0 [M+H^+];
[0210] 3m-Me, ESI-MS m/z: 586.9 [M+H^+].

Example 41

[0211] Compounds of formulae **5k**-**5i** were prepared according to the preparation method of example 2, respectively.

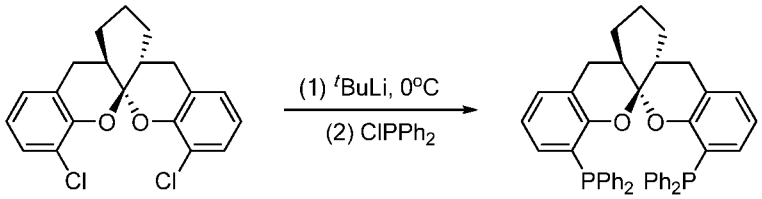


5k **5l** **5i**

[0212] 5k, EI-MS (70 eV) (m/z) 447 (M^+); 51, EI-MS (70 eV) (m/z) 360 (M^+);
[0213] 5i, EI-MS (70 eV) (m/z) 544 (M^+).

Example 42

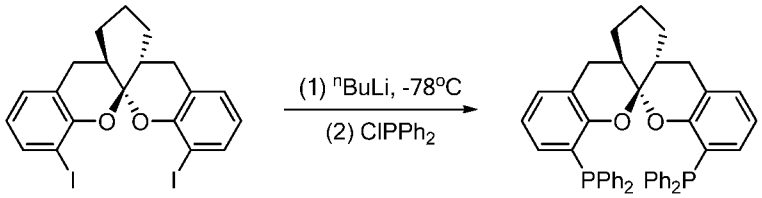
[0214]



[0215] Substrate (*R,R,R*)-**5l** (722 mg, 2.0 mmol) and anhydrous tetrahydrofuran (10 mL) were added to a 50 mL of water-free and oxygen-free Schlenk tube and cooled to below -78 °C. N-butyllithium (4 mL, 1.5 M in pentane, 6.0 mmol) was slowly added dropwise and the reaction mixture was stirred at below -78 °C for 0.5 hr. Chlorodiphenylphosphine (1.1 mL, 6.0 mmol) was slowly added dropwise and then naturally warmed to room temperature. The reaction mixture was stirred at room temperature for 10 hrs. 10 mL of distilled water was added to quench the reaction and the reaction mixture was extracted with dichloromethane (3 × 10 mL). The organic phase was dried on anhydrous sodium sulfate, filtered and concentrated. The residue was purified by column chromatography to obtain target product *(R,R,R)*-**6a** in 65% yield.

Example 43

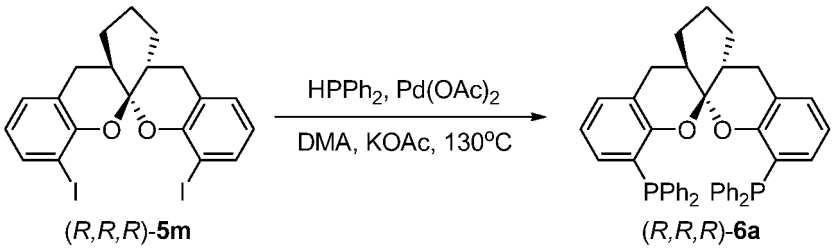
[0216]



[0217] Substrate (*R,R,R*)-**5m** (544 mg, 1.0 mmol) and anhydrous tetrahydrofuran (10 mL) were added to a 50 mL of water-free and oxygen-free Schlenk tube and cooled to below -78 °C. N-butyllithium (1.8 mL, 1.6 M in hexane, 3.0 mmol) was slowly added dropwise and the reaction mixture was stirred at below -78 °C for 0.5 hr. Chlorodiphenylphosphine (0.51 mL, 3.0 mmol) was slowly added dropwise and then naturally warmed to room temperature. The reaction mixture was stirred at room temperature for 10 hrs. 10 mL of distilled water was added to quench the reaction and the reaction mixture was extracted with dichloromethane (3 × 10 mL). The organic phase was dried on anhydrous sodium sulfate, filtered and concentrated. The residue was purified by column chromatography to obtain target product *(R,R,R)*-**6a** in 65% yield.

Example 44

[0218]

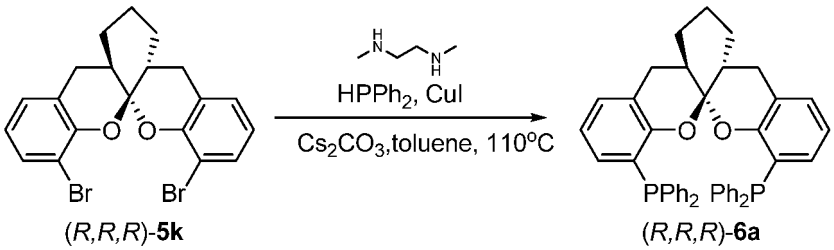


(*R,R,R*)-**5m** (*R,R,R*)-**6a**

[0219] Under argon, palladium acetate (11.2 mg, 0.05 mmol), potassium acetate (215.8 mg, 2.2 mmol), (*R,R,R*)-**5m**(544 mg, 1.0 mmol) and diphenylphosphine(465 mg, 2.5 mmol) were added to a Schelenk tube. Anhydrous *N,N*-dimethylacetamide (DMA, 10 mL) was added and heated to 130°C. The reaction mixture was stirred for 6 hrs and then cooled to room temperature. 10 mL of distilled water was added to quench the reaction. The reaction mixture was extracted with dichloromethane (3×10 mL) and the organic phase was dried on anhydrous sodium sulfate. After filtered and concentrated, the residue was purified by column chromatography to obtain pure bisphosphine ligand *(R,R,R)*-**6a** in 79% yield.

Example 45

[0220]

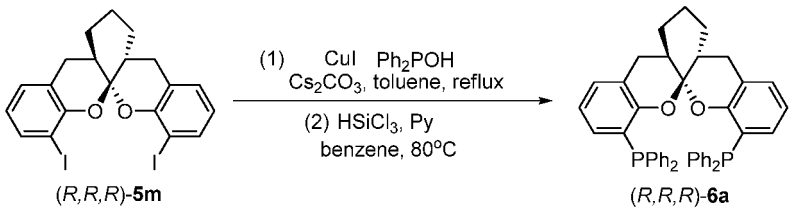


(*R,R,R*)-**5k** (*R,R,R*)-**6a**

[0221] Under argon, cuprous iodide (47.6 mg, 0.25 mmol), cesium carbonate (2.44 g, 7.5 mmol), (*R,R,R*)-**5k** (900 mg, 2.0 mmol), *N,N*-dimethylethanediamine (154.2 mg, 1.75 mmol) and diphenylphosphine (930 mg, 5 mmol) were added to a Schelenk tube. Anhydrous toluene (20 mL) was added and heated to 110 °C. The reaction mixture was stirred for 24 hrs and then cooled to room temperature. 50 mL of distilled water was added to quench the reaction. The reaction mixture was extracted with dichloromethane (3 × 10 mL) and the organic phase was dried on anhydrous sodium sulfate. After filtered and concentrated, the residue was purified by column chromatography to obtain pure bisphosphine ligand *(R,R,R)*-**6a** in 82% yield.

Example 46

[0222]



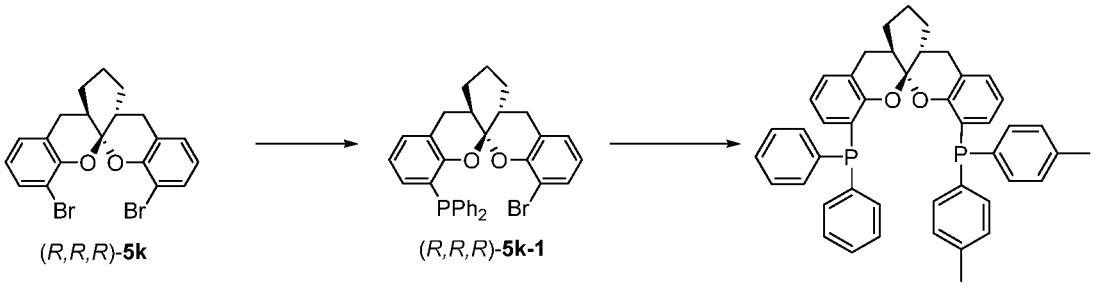
(*R,R,R*)-**5m** (*R,R,R*)-**6a**

[0223] Under argon, cuprous iodide (19.4 mg, 0.1 mmol), cesium carbonate (390 mg, 1.2 mmol), (*R,R,R*)-**5m** (544 mg, 1.0 mmol) and diphenylphosphine oxide (465 mg, 2.5 mmol) were added to a 50 mL Schelenk tube. Anhydrous toluene (10 mL) was added and heated to reflux. The reaction mixture was stirred for 48 hrs and then cooled to room temperature. 10 mL of distilled water was added to quench the reaction. The reaction mixture was extracted with dichlo-

romethane (3 × 20 mL) and the organic phase was dried on anhydrous sodium sulfate. After filtered and concentrated, the residue was purified by column chromatography. The obtained product was directly added to a 50 mL Schelenk tube and anhydrous benzene (10 mL) and pyridine (1.5 mL, 20mmol) were added and cooled to 0 °C. Trichlorosilane (1.0 mL, 10 mmol) was added and the reaction was carried out at 80 °C for 48 hrs. The reaction mixture was cooled to room temperature and saturated sodium bicarbonate aqueous solution (10 mL) was added to quench the reaction. The reaction mixture was extracted with dichloromethane (20mL × 3), and the resulting organic phase was dried on anhydrous sodium sulfate. After filtered and concentrated, the residue was purified by column chromatography to obtain *(R,R,R)*-**6a** as white solid in 62% yield.

Example 47

[0224] (*R,R,R*)-**6p** was prepared according to the following reaction route.



(*R,R,R*)-**5k** (*R,R,R*)-**5k-1** (*R,R,R*)-**6p**

[0225] Substrate(*R,R,R*)-**5k** (350 mg, 0.77 mmol) and anhydrous tetrahydrofuran (6 mL) were added to a 50 mL of water-free and oxygen-free Schlenk tube and cooled to below -78 °C. N-butyllithium (0.48 mL, 1.6 M in hexane, 0.77 mmol) was slowly added dropwise and the reaction mixture was stirred at -78 °C for 0.5 hr. Chlorodiphenylphosphine (0.15 mL, 0.77 mmol) was slowly added dropwise and then naturally warmed to room temperature. The reaction mixture was stirred at room temperature for 10 hrs. 15 mL of distilled water was added to quench the reaction and the reaction mixture was extracted with dichloromethane (3 × 20 mL). The organic phase was dried on anhydrous sodium sulfate, filtered and concentrated. The residue was purified by column chromatography to obtain target product (*R,R,R*)-**5k-1** in 80% yield.

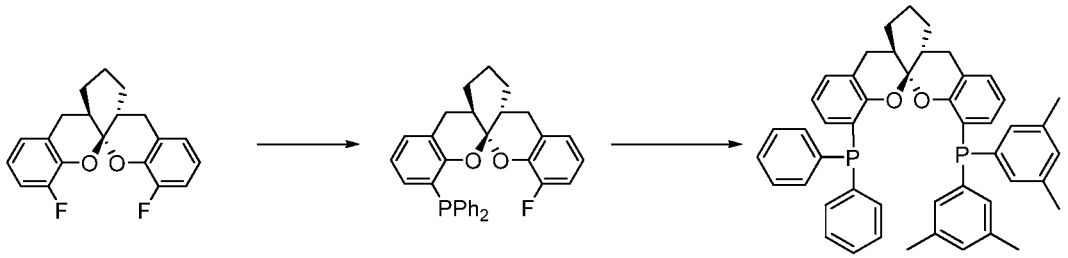
[0226] (*R,R,R*)-**5k-1** (277.7 mg, 0.5 mmol) and anhydrous tetrahydrofuran (6 mL) were added to a 50 mL of water-free and oxygen-free Schlenk tube and cooled to below -78 °C. N-butyllithium (0.31 mL, 1.6 M in hexane, 0.5 mmol) was slowly added dropwise and the reaction mixture was stirred at -78 °C for 0.5 hr. Chlorodi(p-tolyl)phosphine (0.10 mL, 0.5 mmol) was slowly added dropwise and then naturally warmed to room temperature. The reaction mixture was stirred at room temperature for 10 hrs. 15 mL of distilled water was added to quench the reaction and the reaction mixture was extracted with dichloromethane (3 × 20 mL). The organic phase was dried on anhydrous sodium sulfate, filtered and concentrated. The residue was purified by column chromatography to obtain target product (*R,R,R*)-**6p** in 74% yield.

[0227] (*R,R,R*)-**5k-1** white solid, Mp 109-110 °C, $[\alpha]_D^{20}$ = +89.1 (*c* 1.00, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ = 7.92-7.77 (m, 3H), 7.55-7.50 (m, 2H), 7.37-7.24 (m, 8H), 7.04-7.00 (m, 1H), 6.88-6.86 (m, 1H), 6.70-6.66 (m, 1H), 3.04 (dd, *J* = 16.8 Hz, 5.6 Hz, 1H), 2.54-2.40 (3H), 2.09-2.05 (m, 1H), 1.83-1.76 (m, 1H), 1.58-1.56 (m, 1H), 1.44-0.97 (m, 5H) ppm. ^{31}P(162 MHz,$CDCl_3$) δ -15.1 ppm.

[0228] *(R,R,R)*-**6p**, white solid, Mp 99-101 °C, $[\alpha]_D^{20}$ = +129.1 (*c* 1.00, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 7.37-7.21 (m, 22H), 6.68-6.46 (m, 2H), 2.39-2.28 (m, 4H), 2.21 (s, 6H), 1.99-1.87 (m, 2H), 1.32-1.28 (m, 2H), 1.21-1.19 (m, 4H) ppm; ^{31}P(162 MHz,$CDCl_3$) δ -15.3, -19.6 ppm.

Example 48

[0229] (*R,R,R*)-**6q** was prepared according to the following reaction route.



(*R,R,R*)-**5p** (*R,R,R*)-**5p-1** (*R,R,R*)-**6q**

[0230] (*R,R,R*)-**5p** (328 mg, 1.0 mmol), anhydrous tetrahydrofuran (4 mL) and potassium diphenyl phosphine ($KPPh_2$, 2.0 mL, 0.5 mol/L in THF, 1.0 mmol) were added to a 50 mL of water-free and oxygen-free Schlenk tube and heated to reflux for 10 hrs. After cooled, 10 mL of distilled water was added to quench the reaction and the reaction mixture was extracted with dichloromethane (3×10 mL). The organic phase was dried on anhydrous sodium sulfate, filtered and concentrated. The residue was purified by column chromatography to obtain compound (*R,R,R*)-**5p-1** in 74% yield.

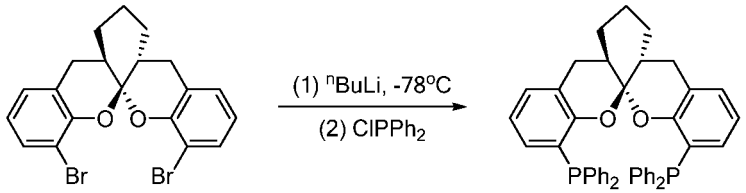
[0231] (*R,R,R*)-**5p-1** (296.7 mg, 0.6 mmol), anhydrous tetrahydrofuran (4 mL), bis(3,5-ditolyl)phosphine (155 mg, 0.6 mmol) and potassium tert-butoxide (67.3 mg, 0.6 mmol) were added to a 50 mL of water-free and oxygen-free Schlenk tube and heated to reflux for 10 hrs. After cooled, 10 mL of distilled water was added to quench the reaction and the reaction mixture was extracted with dichloromethane (3 × 10 mL). The organic phase was dried on anhydrous sodium sulfate, filtered and concentrated. The residue was purified by column chromatography to obtain target product (*R,R,R*)-**6q** in 80% yield.

[0232] (*R,R,R*)-**5p-1** white solid, Mp 107-110 °C, $[\alpha]_D^{20}$ = +104.2 (c 1.10, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ = 7.88-7.7.74 (m, 3H), 7.48-7.34 (m, 9H), 7.03-6.87 (m, 1H), 6.85-6.67 (m, 3H), 2.93 (dd, *J* = 16.4 Hz, 5.2 Hz, 1H), 2.66 (dd, *J* = 16.4 Hz, 6.8 Hz, 1H), 2.44-2.42 (m, 2H), 2.21-2.18 (m, 1H), 1.91-1.85 (m, 1H), 1.70-1.67 (m, 1H), 1.50-1.08 (m, 5H) ppm; ^{31}P(162 MHz,$CDCl_3$) δ -17.1 ppm; ^{19}F-NMR (376 MHz, $CDCl_3$) δ -136.6 ppm.

[0233] *(R,R,R)*-**6q**, Mp 105-107 °C, $[\alpha]_D^{20}$ = +136.6 (c 1.40, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 7.49-7.24 (m, 20H), 6.75-6.59 (m, 2H), 6.21-6.13 (m, 2H), 2.43-2.32 (m, 4H), 2.29 (s, 6H), 2.21 (s, 6H), 2.03-1.98 (m, 2H), 1.35-1.29 (m, 2H), 1.25-1.21 (m, 4H) ppm; ^{31}P(162 MHz,$CDCl_3$) δ -14.5, -20.4 ppm.

Example 49

[0234] *(R,R,R)*-**6a** was prepared according to the following reaction route.

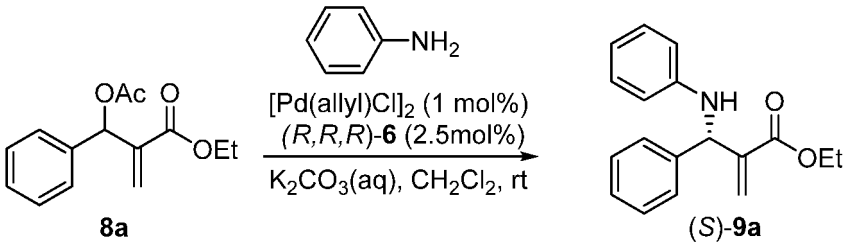


(*R,R,R*)-**5a** (*R,R,R*)-**6a**

[0235] Substrate (*R,R,R*)-**5a** (175 mg, 0.389 mmol) and anhydrous tetrahydrofuran (4 mL) were added to a 10 mL of water-free and oxygen-free Schlenk tube and cooled to below -78°C. N-butyllithium (0.39 mL, 2.5 M in hexane, 0.972 mmol) was slowly added dropwise and the reaction mixture was stirred at -78 °C for 0.5 hr. Chlorodiphenylphosphine (0.18 mL, 0.972 mmol) was slowly added dropwise and then naturally warmed to room temperature. The reaction mixture was stirred at room temperature for 10 hrs. 10 mL of distilled water was added to quench the reaction and the reaction mixture was extracted with dichloromethane (3 × 10 mL). The organic phase was dried on anhydrous sodium sulfate, filtered and concentrated. The residue was purified by column chromatography to obtain target product *(R,R,R)*-**6a** (187 mg, 73% yield).

Example 50

[0236] catalysts were prepared on site by using different bisphosphine ligands (*R,R,R*)-**6** and metal salt $[Pd(r)\text{-}C_3H_5)Cl]_2$ and used in the asymmetric allyl amination of Morita-Baylis-Hillman conjugate **8a** to prepare chiral α-alkylidene-β-amino carboxy acid derivative **9a.**



8a (*S*)-**9a**

[0237] The reaction was conducted as follows: under argon atmosphere, $[Pd(C_3H_5)Cl]_2$(1.8 mg, 0.005 mmol) and bisphosphine ligand (*R,R,R*)-**6** (0.0125 mmol) were separately added to a schlenk tube. Anhydrous CH_2Cl_2 (5 mL) was added and stirred at room temperature for 10 mins to obtain the catalyst. Substrate **8a** (124.1 mg, 0.5 mmol), K_2CO_3 (1.0 M aqueous solution, 1.5 mL, 1.5 mmol) and aniline (140 mg, 1.5 mmol) were successively added and stirred at room temperature for 3 hrs. The reaction mixture was extracted with dichloromethane (3×10 mL), dried on anhydrous sodium sulfate, filtered, concentrated and purified by column chromatography to obtain viscous liquid (*S*)**-9a**. The results of preparing (*S*)-**9a** through asymmetric amination by using **8a** as the substrate and complexs of different bisphosphine ligands (*R,R,R*)-**6** and metal palladium as catalysts were shown in table 2.

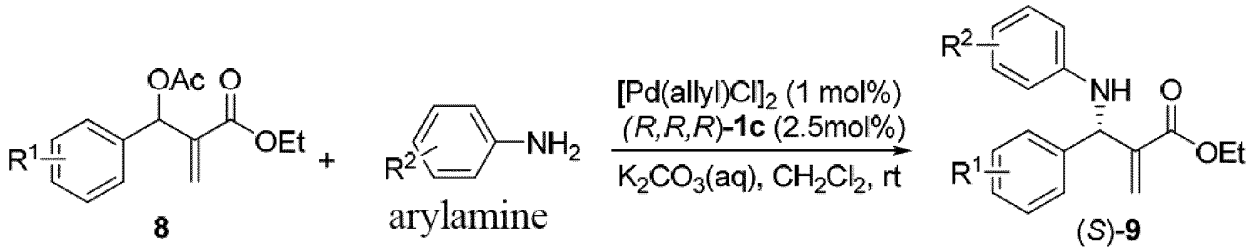
Table 2 results of asymmetric amination

	ligand	yield of (*S*)-**9a**	*ee* (%)
1	*(R,R,R)*-**6a**	90	(+)-94
2	(*R,R,R*)-**6b**	71	(+)-59
3	(*R,R,R*)-**6c**	89	(+)-96
4	(*R,R,R*)-**6d**	89	(+)-95
5	(*R,R,R*)-**6e**	90	(+)-93
6	*(R,R,R)*-**6f**	87	(+)-89
7	*(R,R,R)*-**6g**	88	(+)-90
8	(*R,R,R*)-**6h**	85	(+)-89
9	(*R,R,R*)-**6i**	80	(+)-87
10	(*R,R,R*)-**6j**	82	(+)-93
11	(*R,R,R*)-**6k**	87	(+)-93
12	(*R,R,R*)-**6l**	81	(+)-88
13	(*R,R,R*)-**6m**	79	(+)-87
14	(*S,S,R*)**-6n**	80	(+)-92
15	(*R,R,R*)-**6o**	85	(+)-93
16	(*R,R,R*)-**6p**	89	(+)-91
17	(*R,R,R*)-**6q**	92	(+)-94

[0238] (*S*)-**9a**, $[\alpha]_D^{20}$ = +120.0 (c 1.00, $CHCl_3$), 96% *ee* (determined by high performance liquid chromatography, chiral AD-H column; n-hexane/isobutanol = 95:5, 1.0 mL/min, 254 nm; t_R (major) = 7.07 min; t_R (minor) = 7.81 min). ^1H NMR (400 MHz, $CDCl_3$) δ = 7.38-7.27 (m, 5H), 7.16 (t, *J* = 8.4 Hz, 2H), 6.72 (t, *J* = 7.2 Hz, 1H), 6.57 (d, *J* = 8.8 Hz, 2H), 6.38 (s, 1H), 5.94 (s, 1H), 5.40 (d, *J* = 4.8 Hz, 1H), 4.19-4.09 (m, 3H), 1.20 (t, *J* = 7.2 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 166.1, 146.6, 140.6, 140.2, 129.1, 128.7, 127.7, 127.5, 125.9, 117.8, 113.3, 60.7, 59.0, 14.0 ppm.

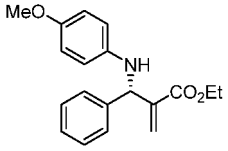
Example 51

[0239] The catalyst was prepared on site by using bisphosphine ligand *(R,R,R)*-**6c** and metal $[Pd(C_3H_5)Cl]_2$ to catalyze asymmetric allyl amination of Morita-Baylis-Hillman adduct **8**.The reaction equation was shown as follows.

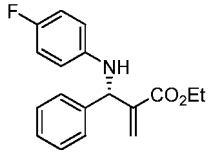


8 (S)-9

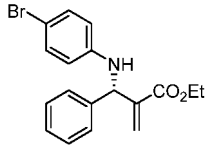
[0240] The reaction was conducted as follows: under argon atmosphere, $[Pd(C_3H_5)Cl]_2$(1.8 mg, 0.005 mmol) and (*R,R,R*)-**6c** (9.6mg, 0.0125 mmol) were separately added to a schlenk tube. Anhydrous CH_2Cl_2 (5 mL) was added and stirred at room temperature for 10 mins. Substrate **8** (0.5 mmol), K_2CO_3 (1.0 M aqueous solution, 1.5 mL, 1.5 mmol) and arylamine (1.5 mmol) were successively added and stirred at room temperature for 3 hrs. The reaction mixture was extracted with dichloromethane (3×10 mL), dried on anhydrous sodium sulfate, filtered, concentrated and purified by column chromatography to obtain chiral amination product (*S*)-**9**. The results were shown as follows.



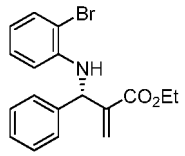
[0241] (*S*)-**9b**, colourless liquid, 88% yield, $[\alpha]_D^{20}$ = +98.4 (c 1.00, $CHCl_3$), 95% *ee* (determined by high performance liquid chromatography, chiral AD-H column; n-hexane/isobutanol = 95:5, 1.0 mL/min, 254 nm; t_R (major) = 11.08 min; t_R (minor) = 12.12 min). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.38-7.25 (m, 5H), 6.75 (d, *J*= 8.8 Hz, 2H), 6.54 (d, *J*= 9.2 Hz, 2H), 6.37 (s, 1H), 5.93 (s, 1H), 5.32 (s, 1H), 4.18-4.09 (m, 2H), 3.94 (s, 1H), 3.72 (s, 3H), 1.20 (t, *J* = 7.2 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 166.2, 152.2, 141.0, 140.9, 140.5, 128.6, 127.6, 127.4, 125.8, 114.7, 114.6, 60.7, 59.7, 55.7, 14.0 ppm.



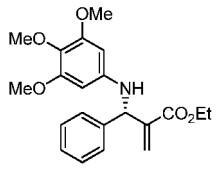
[0242] (*S*)-**9c**, colourless liquid, 89% yield, $[\alpha]_D^{20}$ = +78.9 (c 1.00, $CHCl_3$), 95% ee (determined by high performance liquid chromatography, chiral AD-H column; n-hexane/isobutanol = 99:1, 1.0 mL/min, 254 nm; t_R (major) = 18.31 min; t_R (minor) = 22.32 min). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.37-7.25 (m, 5H), 6.86 (t, *J*= 8.8 Hz, 2H), 6.51-6.48 (m, 2H), 6.37 (s, 1H), 5.89 (s, 1H), 5.33 (s, 1H), 4.16-4.13 (m, 2H), 4.08 (s, br, 1H), 1.21 (t, *J* = 7.2 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 166.1, 155.9 (d, $J_{(F,C)}$= 234.0 Hz), 143.0 (d, $J_{(F,C)}$= 1.8 Hz), 140.4 (d, $J_{(F,C)}$= 23.4 Hz), 128.7 (s), 127.7 (s), 127.4 (s), 125.9 (s), 115.6 (s), 115.4 (s), 114.2 (d, $J_{(F,C)}$= 7.4 Hz), 60.8, 59.5, 14.0 ppm; ^{19}F-NMR (376 MHz, $CDCl_3$) δ -127.4 ppm.



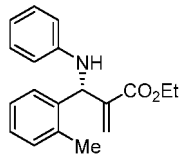
[0243] (*S*)-**9d**, white solid, 83% yield. Mp 78-80 °C, $[\alpha]_D^{20}$ = +115.0 (c 1.00, $CHCl_3$), 95% *ee* (determined by high performance liquid chromatography, chiral AD-H column; n-hexane/isobutanol = 98:2, 1.0 mL/min, 254 nm; t_R (major) = 16.31 min; t_R (minor) = 18.01 min). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.33-7.19 (m, 7H), 6.42 (d, *J* = 8.8 Hz, 2H), 6.36 (s, 1H), 5.85 (s, 1H), 5.35 (s, 1H), 4.16-4.05 (m, 3 H), 1.18 (t, *J*= 7.2 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 165.9, 145.5, 140.0, 139.8, 131.7, 128.6, 127.7, 127.3, 125.9, 114.9, 109.3, 60.7, 58.8, 13.9 ppm. The absolute configuration of obtained compound **9d** was (S) determined by X-ray crystal diffraction diagram and the absolute configurations of other chiral α-alkylidene-β-amino carboxy acid derivatives **9a-9c** and **9e-9k** were determined by comparision of Cotton effect with (*S*)-**9d**.



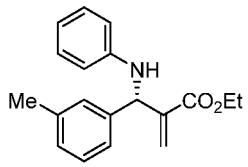
[0244] (*S*)-**9e**, colourless liquid, 67% yield, $[\alpha]_D^{20}$ = +53.3 (*c* 1.00, $CHCl_3$), 96% *ee* (determined by high performance liquid chromatography, chiral AD-H column; n-hexane/isobutanol = 99:1, 1.0 mL/min, 254 nm; t_R (major) = 7.96 min; t_R (minor) = 8.76 min). ^1H NMR (400 MHz, $CDCl_3$) δ = 7.43-7.25 (m, 6H), 7.11 (t, *J*= 10.8 Hz, 1H), 6.59-6.54 (m, 2H), 6.38 (s, 1H), 5.85 (s, 1H), 5.49 (d, *J*= 8.0 Hz, 1 H), 4.87 (d, *J* = 7.6 Hz, 1H), 4.21-4.10 (m, 2H), 1.20 (t, *J* = 9.2 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 165.9, 143.4, 140.0, 139.9, 132.2, 128.7, 128.3, 127.8, 127.3, 125.9, 118.2, 112.4, 109.8, 60.8, 58.5, 13.9 ppm.



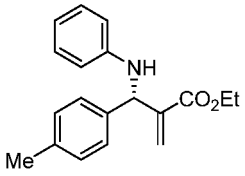
[0245] (*S*)-**9f**, colourless liquid, 85% yield, $[\alpha]_D^{20}$ = +86.6 (c 1.00, $CHCl_3$), 96% *ee* (determined by high performance liquid chromatography, chiral AD-H column; n-hexane/isobutanol = 85:15, 1.0 mL/min, 254 nm; t_R (major) = 10.38 min; t_R (minor) = 12.36 min). ^1H NMR (400 MHz, $CDCl_3$) δ = 7.38-7.24 (m, 5H), 6.39 (s, 1H), 5.95 (s, 1H), 5.82 (s, 2H), 5.40 (s, 1H), 4.19-4.10 (m, 3H), 3.73 (s, 9H), 1.20 (t, *J* = 7.2 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 166.0, 153.5, 143.3, 140.4, 130.0, 128.5, 127.5, 127.2, 125.7, 90.8, 60.7, 60.6, 59.0, 55.6, 13.8 ppm.



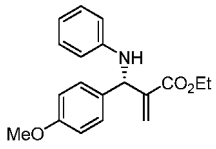
[0246] (*S*)-**9g**, white solid, 64% yield. Mp 93-94 °C, $[\alpha]_D^{20}$ = +146.5 (*c* 1.00, $CHCl_3$), 91% *ee* (determined by high performance liquid chromatography, chiral AD-H column; n-hexane/isobutanol = 98:2, 1.0 mL/min, 254 nm; t_R (major) = 6.91 min; t_R (minor) = 8.44 min). ^1H NMR (400 MHz, $CDCl_3$) δ = 7.24-7.13 (m, 6H), 6.71 (t, *J*= 7.2 Hz, 1H), 6.55 (d, *J* = 8.0 Hz, 2H), 6.43 (s, 1H), 5.89 (s, 1H), 5.60 (s, 1H), 4.20-4.07 (m, 2H), 3.85 (s, br, 1H), 2.40 (s, 3H), 1.18 (t, *J* = 7.2 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 166.4, 146.8, 140.0, 138.7, 136.7, 130.7, 129.1, 127.7, 126.3, 126.2, 126.0, 117.6, 112.8, 60.7, 54.7, 19.1, 14.0 ppm.



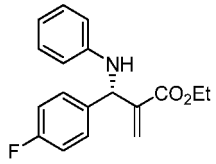
[0247] (*S*)-**9h**, white solid, 89% yield. Mp 56-57 °C, $[\alpha]_D^{20}$ = +131.8 (c 1.00, $CHCl_3$), 97% *ee* (determined by high performance liquid chromatography, chiral AD-H column; n-hexane/isobutanol = 98:2, 1.0 mL/min, 254 nm; t_R (major) = 9.52 min; t_R (minor) = 11.05 min). ^1H NMR (400 MHz, $CDCl_3$) δ = 7.21-7.07 (m, 6H), 6.70 (t, *J* = 7.6 Hz, 1H), 6.56 (d, *J* = 8.4 Hz, 2H), 6.37 (s, 1H), 5.93 (s, 1H), 5.36 (s, 1H), 4.19-4.08 (m, 3H), 2.33 (s, 3H), 1.20 (t, *J* = 7.2 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 166.2, 146.7, 140.6, 140.2, 138.3, 129.1, 128.5, 128.4, 128.2, 125.7, 124.5, 117.7, 113.3, 60.7, 58.9, 21.4, 14.0 ppm.



[0248] (*S*)-**9i**, colourless liquid, 90% yield, $[\alpha]_D^{20}$ = +129.6 (c 1.00, $CHCl_3$), 95% *ee* (determined by high performance liquid chromatography, chiral AD-H column; n-hexane/isobutanol = 98:2, 1.0 mL/min, 254 nm; t_R (major) = 12.55 min; t_R (minor) = 14.98 min). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.26-7.22 (m, 2H), 7.16-7.12 (m, 4H), 6.70 (t, *J* = 8.4 Hz, 1H), 6.56 (d, *J* = 8.4 Hz, 2H), 6.36 (s, 1H), 5.92 (s, 1H), 5.36 (s, 1H), 4.18-4.09 (m, 3H), 2.32 (s, 3H), 1.21 (t, *J*= 7.6 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 166.2, 146.7, 140.3, 137.7, 137.4, 129.3, 129.1, 127.4, 125.5, 117.7, 113.3, 60.7, 58.6, 21.0, 14.0 ppm.



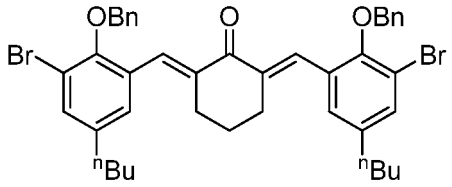
[0249] (*S*)-**9j**, colourless liquid, 96% yield, $[\alpha]_D^{20}$ = +132.6 (c 1.00, $CHCl_3$), 95% *ee* (determined by high performance liquid chromatography, chiral AD-H column; n-hexane/isobutanol = 98:2, 1.0 mL/min, 254 nm; t_R (major) = 20.63 min; t_R (minor) = 23.04 min). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.28 (d, *J* = 8.4 Hz, 2H), 7.15 (t, *J* = 7.6 Hz, 2H), 6.86 (d, *J* = 8.4 Hz,2H), 6.71 (t, *J* = 7.2 Hz, 1H), 6.56 (d, *J* = 8.0 Hz, 2H), 6.35 (s, 1H), 5.92 (s, 1H), 5.35 (s, 1H), 4.19-4.09 (m, 3H), 3.78 (s, 3H), 1.21 (t, *J* = 7.2 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 166.2, 159.0, 146.7, 140.3, 132.7, 129.0, 128.6, 125.3, 117.7, 114.0, 113.3, 60.7, 58.3, 55.2, 14.0 ppm.



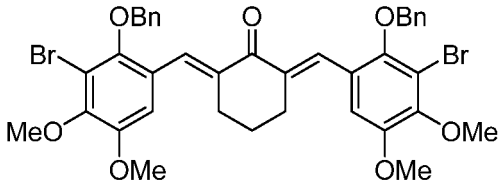
[0250] (*S*)-**9k**, colourless liquid, 96% yield, $[\alpha]_D^{20}$ = +89.9 (*c* 1.00, $CHCl_3$), 97% *ee* (determined by high performance liquid chromatography, chiral AD-H column; n-hexane/isobutanol = 98:2, 1.0 mL/min, 254 nm; t_R (major) = 12.72 min; t_R (minor) = 13.89 min). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.35-7.32 (m, 2H), 7.16 (t, *J* = 8.0 Hz, 2H), 7.01 (t, *J* = 8.8 Hz, 2H), 6.73 (t, *J* = 7.2 Hz, 1H), 6.57 (d, *J* = 8.0 Hz, 2H), 6.38 (s, 1H), 5.92 (s, 1H), 5.38 (s, 1H), 4.18-4.13 (m, 3H), 1.21 (t, *J*= 6.8 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 166.0, 162.2 (d, $J_{(F,C)}$= 244.0 Hz), 146.5 (s), 140.1 (s), 136.4 (d, $J_{(F,C)}$= 2.9 Hz), 129.1 (d, $J_{(F,C)}$= 7.8 Hz), 126.0 (s), 118.0 (s), 115.6 (s), 115.4 (s), 113.4 (s), 60.8, 58.3, 14.0 ppm; ^{19}F-NMR (376 MHz, $CDCl_3$) δ -114.6 ppm.

Example 52

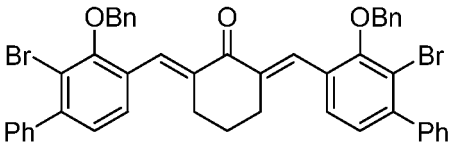
[0251] Compounds of formulae **3n-Bn - 3p-Bn** were prepared according to the preparation method of example 1, respectively.



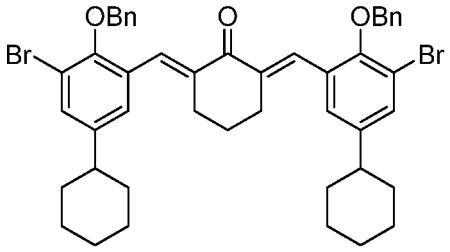
3n-Bn



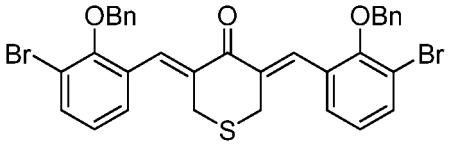
30-Bn



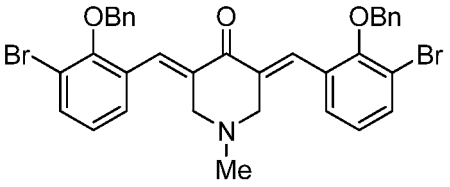
3p-Bn



3q-Bn



3r-Bn

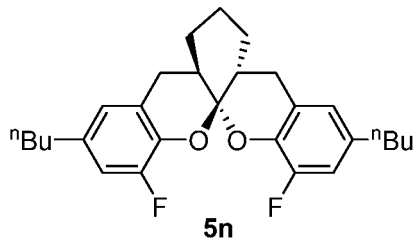


3s-Bn

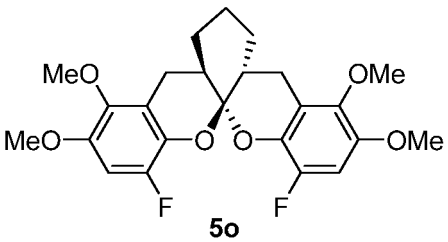
[0252] 3n-Bn, ESI-MS m/z: 555.1 [M+H$^+$]; 3o-Bn, ESI-MS m/z: 763.0 [M+H$^+$];
[0253] 3p-Bn, ESI-MS m/z: 795.1 [M+H$^+$]; 3q-Bn, ESI-MS m/z: 807.1 [M+H$^+$];
[0254] 3r-Bn, ESI-MS m/z: 660.0 [M+H$^+$]; 3s-Bn, ESI-MS m/z: 658.0 [M+H$^+$].

Example 53

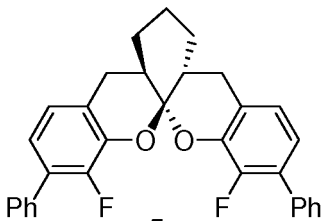
[0255] Compounds of formulae (*R,R,R*)-**5n** - (*R,R,R*)-**5s** were prepared according to the preparation method of example 5 by using compounds 3n-Bn - 3s-Bn as raw meterial, respectively.



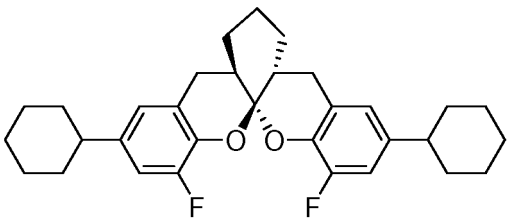
5n



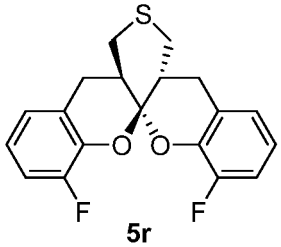
5o



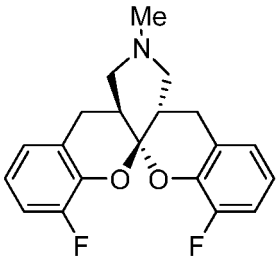
5p



5q



5r



5s

[0256] 5n, EI-MS (70 eV) (m/z) 440 (M^+); 5o, EI-MS (70 eV) (m/z) 448 (M^+);

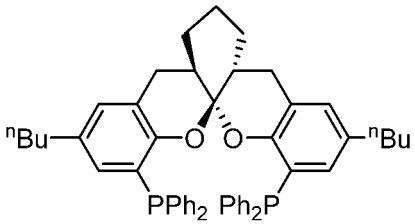
[0257] 5p, EI-MS (70 eV) (m/z) 480 (M^+); 5q, EI-MS (70 eV) (m/z) 492 (M^+);

[0258] 5r, EI-MS (70 eV) (m/z) 346 (M^+); 5s, EI-MS (70 eV) (m/z) 343 (M^+).

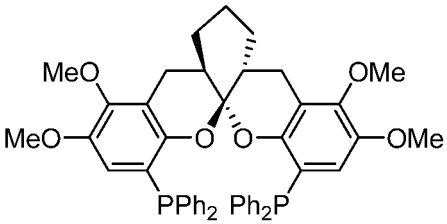
[0259] Similarly, cpmpounds of formulae *(S,S,S)*-**5n** - *(S,S,S)*-**5s** were prepared according to the preparation method of example 16 by using compounds 3n-Bn - 3s-Bn as raw meterial, respectively.

Example 54

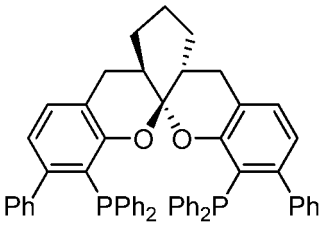
[0260] Compounds of formulae *(R,R,R)*-**6r** - *(R,R,R)*-**6w** were prepared according to the preparation method of example 16 by using compounds *(R,R,R)*-**5n** - (*R,R,R*)-**5s** as raw meterial, respectively.



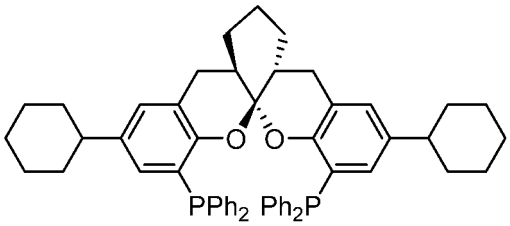
6r



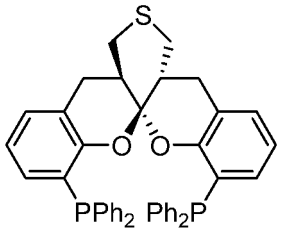
6s



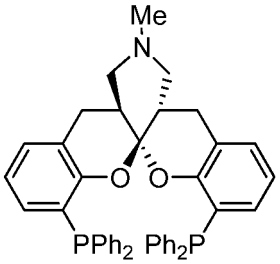
6t



6u



6v



6w

[0261] 6r, ESI-MS m/z: 773.8 [M+H$^+$]; 6s, ESI-MS m/z: 781.5 [M+H$^+$];

[0262] 6t, ESI-MS m/z: 813.4 [M+H$^+$], 835.2 [M+Na$^+$]; 6u, ESI-MS m/z: 826.2 [M+H$^+$];

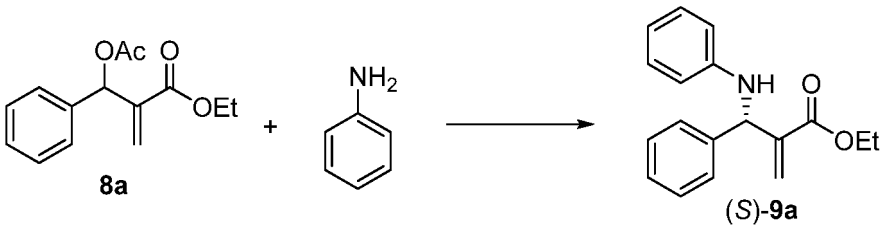
[0263] 6v, ESI-MS m/z: 679.9 [M+H$^+$]; 6w, ESI-MS m/z: 676.8 [M+H$^+$].

[0264] Compounds of formulae *(S,S,S)*--**6r** - *(S,S,S)*-**6w** were prepared according to the preparation method of example 41 by using compounds *(S,S,S)*-**5n** - (*S,S,S*)-**5s** as raw meterial, respectively.

[0265] Racemic **6r - 6w** compounds were prepared according to the preparation method of example 43 by using racemic compounds **5k** - **5p** as raw meterial, respectively.

Example 55

[0266] The catalyst was prepared on site by using ligands *(R,R,R)*-6r-*(R,R,R)*-6w and metal salt $[Pd(r)\text{-}C_3H_5)Cl]_2$, and used in asymmetric allyl amination of Morita-Baylis-Hillman conjugate **8** to prepare chiral α-alkylidene-β-amino carboxy acid derivative **9a.**



8a (*S*)-**9a**

[0267] The reaction was conducted as follows: under argon atmosphere, $[Pd(C_3H_5)Cl]_2$ (1.8 mg, 0.005 mmol) and bisphosphine ligands (*R,R,R*)-**6** k-6p(0.0125 mmol) were separately added to a schlenk tube. Anhydrous CH_2Cl_2 (5 mL) was added and stirred at room temperature for 10 mins to obtain the catalyst. Substrate **8a** (124.1 mg, 0.5 mmol), K_2CO_3 (1.0 M aqueous solution, 1.5 mL, 1.5 mmol) and aniline (140 mg, 1.5 mmol) were successively added and stirred at room temperature for 3 hrs. The reaction mixture was extracted with dichloromethane (3×10 mL), dried on anhydrous sodium sulfate, filtered, concentrated and purified by column chromatography to obtain viscous liquid (*S*)-**9a**.

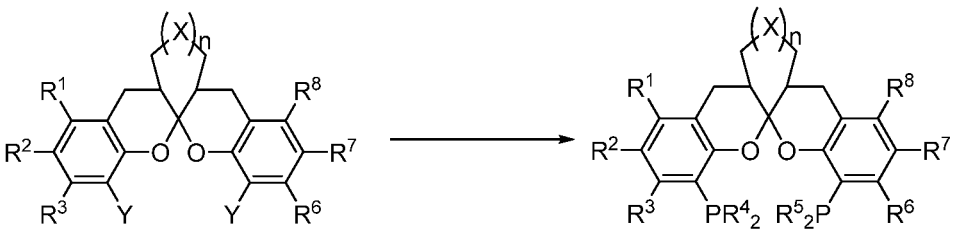
Table 3 results of asymmetric amination

	ligand	yield of (*S*)-**9a** (%)	*ee* (%)
1	*(R,R,R)*-**6r**	89	(+)-91
2	(*R,R,R*)-**6s**	91	(+)-92
3	*(R,R,R)*-**6t**	85	(+)-88
4	(*R,R,R*)-**6u**	83	(+)-93
5	(*R,R,R*)-**6v**	90	(+)-90
6	(*R,R,R*)-**6w**	88	(+)-92

[0268] All literatures mentioned in the present application are incorporated by reference herein, as though individually incorporated by reference. Additionally, it should be understood that after reading the above teaching, many variations and modifications may be made by the skilled in the art, and these equivalents also fall within the scope as defined by the appended claims.

Claims

1. A preparation method for a compound of formula I, comprising the step of synthetizing the compound of formula I from a compound of formula II,



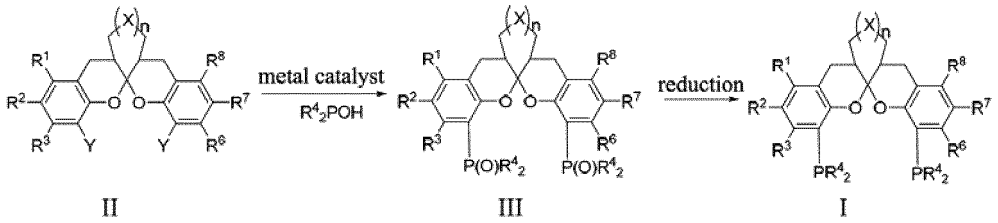
II I

wherein R^1, R^2, R^3, R^6, R^7 and R^8 are independently selected from a hydrogen, a halogen, substituted or

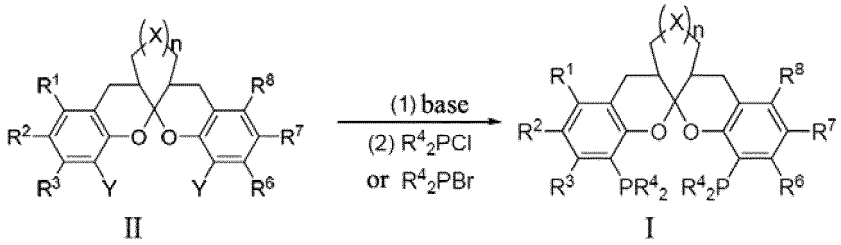
unsubstituted following groups: a C_1-C_{10} alkyl, a C_1-C_4 alkoxyl, a C_3-C_{30} cycloalkyl or an aryl;
R^4 and R^5 are independently selected from substituted or unsubstituted following groups: a C_3-C_{10} cycloalkyl, a C_1-C_{10} alkyl, 2-furyl, or an aryl;
X is selected from CH_2, NH, NCH_3, O or S; n=0-4;
wherein the substitution refers to be substituted by the following substituents: a halogen, a C_1-$_6$ alkyl, a C_1-$_6$ haloalkyl, or a C_1-$_6$ alkoxyl;
Y is F, Cl, Br or I.

2. The preparation method of claim 1, wherein R^5 and R^4 are the same and the method includes the following steps:

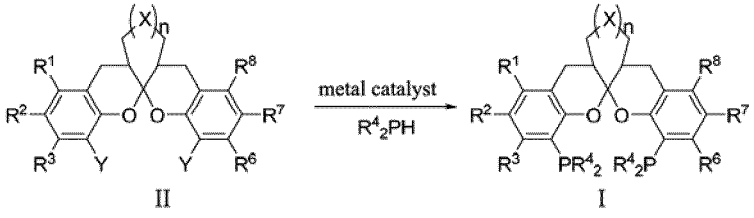
(a1) the compound of formula II reacts with $R^4{}_2POH$ in an organic solvent under the action of a metal catalyst to obtain a compound of formula III;
(b1) the compound of formula III is reduced to obtain the ligand,



or includes the following step:
(a2) in an organic solvent and under the action of a base, Y group is removed from the compound of formula II and then the compound of formula II reacts with $R^4{}_2PCl$ or $R^4{}_2PBr$ to obtain the ligand,



or includes the following step:
(a3) the compound of formula II reacts with $R^4{}_2PH$ in an organic solvent and under the action of a metal catalyst to obtain the ligand;



wherein Y is Cl, Br or I; R^1, R^2, R^3, R^4, R^6, R^7, R^8, X and n are defined as in claim 1.

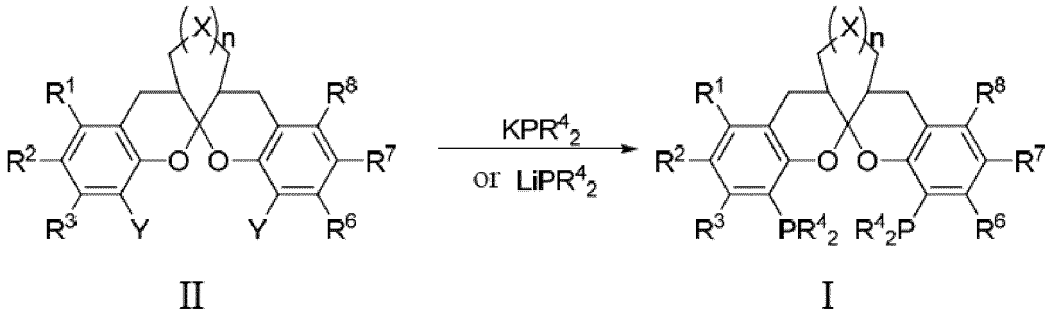
3. The preparation method of claim 2, wherein, in step (a2), the mole ratio of the base to the compound of formula II is 2: 1 - 10: 1; and the mole ratio of $R^4{}_2PCl$ or $R^4{}_2PBr$ to the compound of formula II is 2: 1 - 10: 1; or
in step (a3), the mole ratio of the metal catalyst to the compound of formula II is 0.001 - 0.5: 1; and the mole ratio of $R^4{}_2PH$ to the compound of formula II is 2 - 10: 1.

4. The preparation method of claim 2, wherein said metal catalyst is at least one selected from $Pd(OAc)_2$, $PdCl_2$,

$Pd_2(dba)_3$, $Pd(dba)_2$, $[Pd(C_3H_5)Cl]_2$, $Pd(PPh_3)_4$, $Pd(PPh_3)_2Cl_2$, $Pd(CH_3CN)Cl_2$, dpppNiCl$_2$, $Ni(PPhI)_2Cl_2$, CuI or a combination thereof.

5. The preparation method of claim 2, wherein, in step (a1), the mole ratio of the metal catalyst to the compound of formula II is 0.001 - 0.5: 1; and the mole ratio of $R^4{}_2POH$ to the compound of formula II is 2 - 10: 1; and/or in step (b1), the reducing agent is one selected from $HSiCl_3$, $(Me_2SiH)_2O$, $LiAlH_4$, $(EtO)_3SiH$ or a combination thereof.

6. The preparation method of claim 1, wherein R5 and R4 are the same, and the method comprises the following step:

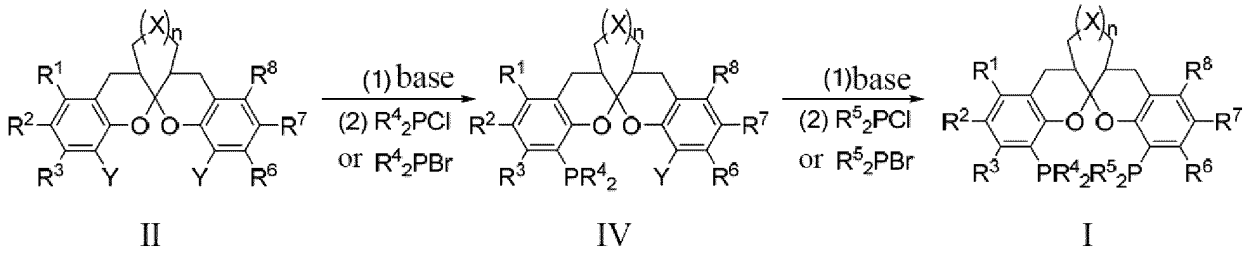


II I

the compound of formula II reacts with $KPR^4{}_2$ or $LiPR^4{}_2$ in an organic solvent to form the ligand, wherein Y is F; R^1, R^2, R^3, R^4, R^6, R^7, R^8, X and n are defined as in claim 1.

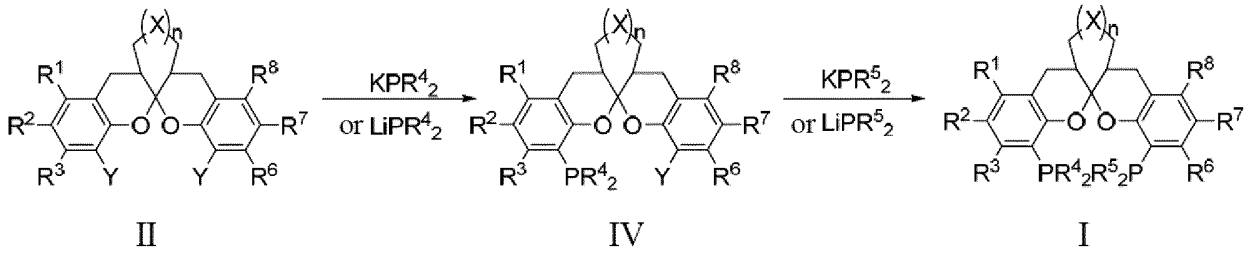
7. The preparation method of claim 6, wherein the mole ratio of $KPR^4{}_2$ or $LiPR^4{}_2$ to the compound of formula II is 2: 1 - 10: 1.

8. The preparation method of claim 1, wherein the method comprises the following steps:



II IV I

(i1) in an organic solvent, the compound of formula II reacts with a base and then reacts with $R^4{}_2PCl$ or $R^4{}_2PBr$ to form a compound of formula IV;
(ii1) the compound of formula IV reacts with a base and then reacts with $R^5{}_2PCl$ or $R^5{}_2PBr$ to form the ligand, wherein Y is Cl, Br or I;
R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, X and n are defined as in claim 1 and $R^4 \neq R^5$;
or comprises the following steps:



II IV I

(i2) in an organic solvent, the compound of formula II reacts with $KPR^4{}_2$ or $LiPR^4{}_2$ to form a compound of formula IV;

(ii2) the compound of formula IV reacts with KPR^5_2 or $LiPR^5_2$ to form the ligand,

wherein Y is F; R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, X and n are defined as in claim 1, and $R^4 \neq R^5$.

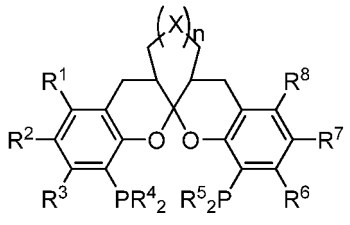
9. The preparation method of claim 8, wherein, in step (i1), the mole ratio of the base to the compound of formula II is 1: 1 - 1.2: 1; and the mole ratio of R^4_2PCl or R^4_2PBr to the compound of formula II is 1: 1 - 1.2: 1; and/or
in step (ii1), the mole ratio of the base to the compound of formula IV is 1: 1 - 1.2: 1; and the mole ratio of R^5_2PCl or R^5_2PBr to the compound of formula IV is 1: 1 - 1.2: 1.

10. The preparation method of claim 8, wherein, in step (i2), the mole ratio of KPR^4_2 or $LiPR^4_2$ to the compound of formula II is 1: 1 - 1.2: 1; and/or
in step (ii2), the mole ratio of KPR^5_2 or $LiPR^5_2$ to the compound of formula IV is 1: 1 - 1.2: 1.

11. The preparation method of claim 2, 6 or 8, wherein said organic solvent is one of benzene, toluene, xylene, dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane, diethyl ether, tetrahydrofuran, methanol, ethanol, *N,N*-dimethyl formamide or dimethyl sulfoxide, or a mixture thereof.

12. The preparation method of claim 2, 6 or 8, wherein said base is selected from n-butyl lithium, tert-butyl lithium, cyclohexyl lithium, methyl lithium, isopropyl lithium, lithium bis(trimethylsilyl)amide, sodium bis(trimethylsilyl)amide, potassium bis(trimethylsilyl)amide, ethyl magnesium chloride, ethyl magnesium bromide, phenyl magnesium chloride, phenyl magnesium bromide.

13. A ligand having a structure as shown in general formula I:



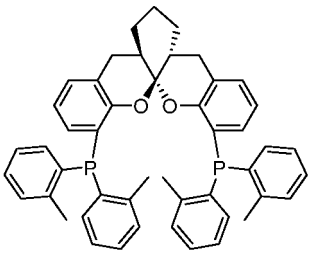
(I)

wherein,

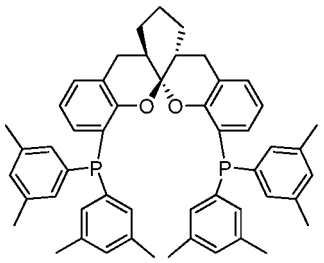
R^1, R^2, R^3, R^6, R^7 and R^8 are independently selected from a hydrogen, a halogen, substituted or unsubstituted following groups: a C_1-C_{10} alkyl, a C_1-C_4 alkoxyl, a C_3-C_{30} cycloalkyl or an aryl;
R^4 and R^5 are independently selected from substituted or unsubstituted following groups: a C_3-C_{10} cycloalkyl, a C_1-C_{10} alkyl, 2-furyl, or an aryl;
X is selected from CH_2, NH, NCH_3, O or S; n=0 - 4;
wherein the substitution refers to be substituted by the following substituents: a halogen, a $C_{1\text{-}6}$ alkyl, a $C_{1\text{-}6}$ haloalkyl, or a $C_{1\text{-}6}$ alkoxyl,
provided that not both of R^4 and R^5 are phenyl, when all of R^1, R^2, R^3, R^6, R^7 and R^8 are hydrogen, X is CH_2 and n=1.

14. The ligand according to claim 13, wherein R^1, R^2, R^3, R^6, R^7 and R^8 are independently selected from a hydrogen, a C_1-C_6 alkyl, a C_1-C_4 alkoxyl, a C_3-C_{10} cycloalkyl, a phenyl or a halogen;
R^4, R^5 are independently selected from a substituted phenyl, a C_3-C_6 cycloalkyl or a C_2-C_6 alkyl, and the substitution is mon-substituted, di-substituted or tri-substituted by the following substituents: a halogen, a $C_{1\text{-}6}$ alkyl, a $C_{1\text{-}6}$ haloalkyl, or a $C_{1\text{-}6}$ alkoxyl;
X is selected from CH_2, O, NCH_3 or S;
provided that not both of R^4 and R^5 are phenyl, when all of R^1, R^2, R^3, R^6, R^7 and R^8 are hydrogen, X is CH_2 and n=1.

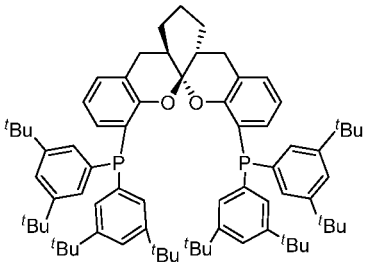
15. The ligand according to claim 13, wherein the ligand is any one selected from compounds of formulae 6b~6w, or enantiomers, racemates or diastereoisomers of the compounds of formulae 6b~6w:



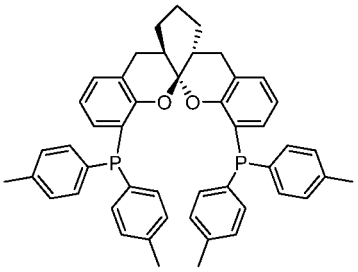
6b



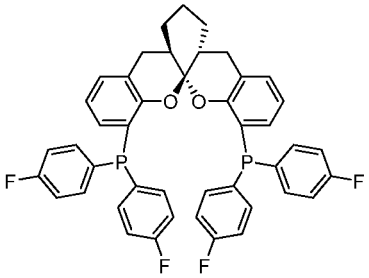
6c



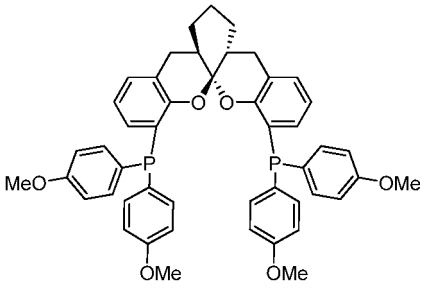
6d



6e



6f



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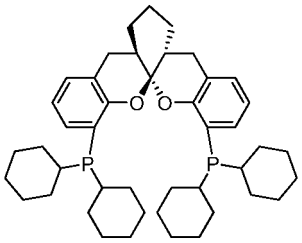

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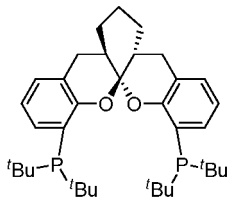

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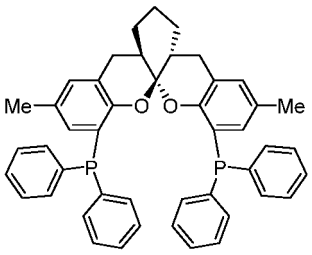

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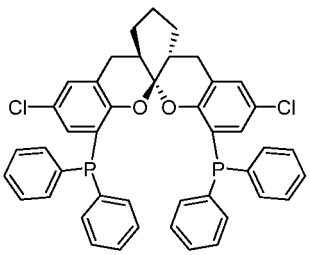

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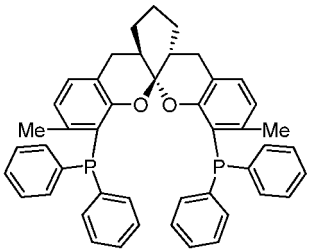

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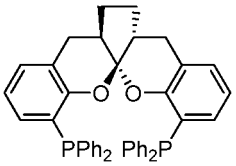

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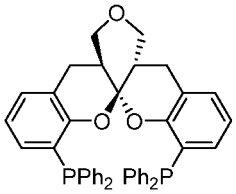

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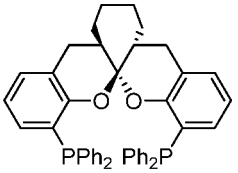

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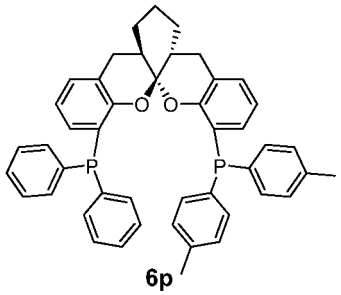

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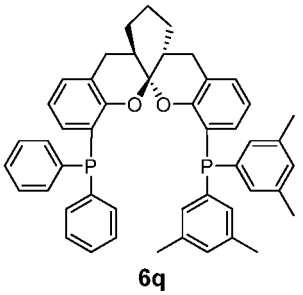

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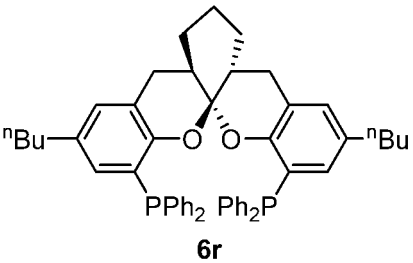

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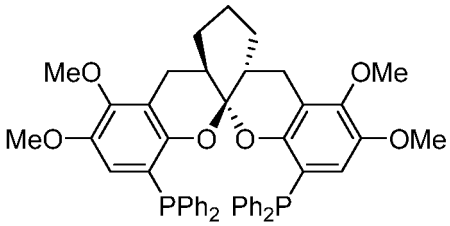

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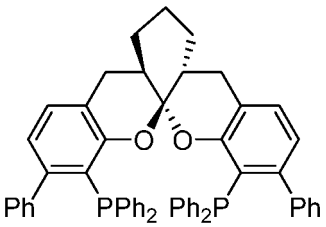

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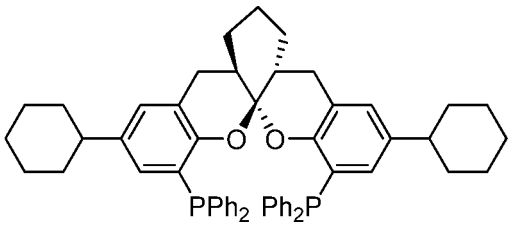

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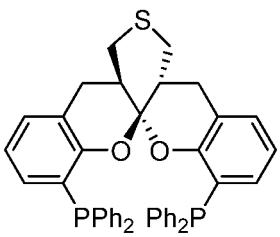

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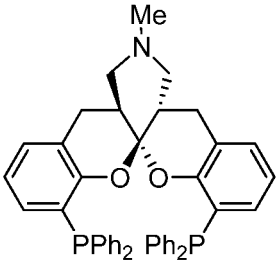
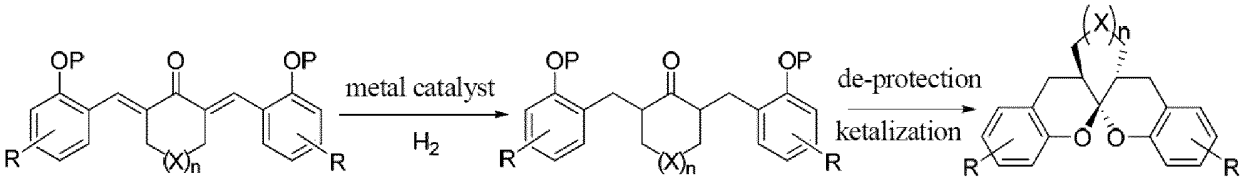


6w

16. Use of the ligand according to claim 13 for a catalyst or for synthesizing a catalyst.

17. A preparation method for chiral aromatic spiroketal compounds comprising the following steps:



3-P 4-P V

(a) under hydrogen atmosphere, a compound of formula **3-P** as a substrate is subjected to catalytic hydrogenation in an organic solvent by using a metal complex as a catalyst to obtain a hydrogenated product, a compound of formula **4-P;**

(b) protecting groups are removed from the compound of formula **4-P,** and then the compound is subjected to ketalization to obtain the chiral aromatic spiroketal compound, wherein the chiral aromatic spiroketal compound is a compound of general formula V or an enantiomer, racemate or diastereoisomer thereof,

wherein X is selected from CH_2, NH, NCH_3, O or S; n= 0 - 4; R on the left is one or more of R^{11}, R^{12}, R^{13} and R^{14} R on the right is one or more of R^{15}, R^{16}, R^{17} and R^{18}, and R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17} and R^{18} are independently selected from a hydrogen, a C_1-C_{10} alkyl, a C_1-C_4 alkoxyl, a C_3-C_{30} cycloalkyl, a halogen or an aryl;
P is a methyl, a benzyl, a p-methoxy benzyl, a tert-butyl, a tert-butyldimethylsilyl, a tert-butyldiphenylsilyl, an allyl, a methoxymethyl, a methylthiomethyl, a methoxyethoxymethyl, a benzyloxymethyl, a tetrahydro 2-pyranyl or ester

group.

18. The preparation method of claim 17, wherein the mole ratio of the compound of formula **3-P** to the metal complex catalyst is 10000: 1 - 10: 1.

19. The preparation method of claim 17, wherein the metal complex is a complex of metal rhodium, ruthenium, palladium or iridium.

20. The preparation method of claim 17, wherein the metal complex is a complex of phosphine-nitrogen ligand and iridium.

21. The preparation method of claim 17, wherein the catalytic hydrogenation reaction is carried out under 1-100 normal atmospheric pressure of hydrogen at -78 - 80 °C for 1-48 hrs.

22. The preparation method of claim 17, wherein said organic solvent is at least one of benzene, toluene, xylene, dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane, diethyl ether, tetrahydrofuran, methanol, ethanol, *N,N*-dimethyl formamide and dimethyl sulfoxide.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CN2013/071091

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Claims 1 to 16, which related to compounds of formula I as catalysts of asymmetrical reactions, preparation methods and uses thereof. Claims 17 to 22, which related to preparation methods of chiral aromatic spiroketal compounds formula V. The common technical feature of the two inventions is compounds with structure of dihydrobenzofuran spiroketal. However, compounds with structure of dihydrobenzofuran spiroketal are known in this art (see CN 102424682 A), thus this common feature cannot be considered as a special technical feature within the meaning of PCT Rule 13. 2. Therefore the two inventions are not so linked as to form a single general inventive concept, as required by PCT Rule 13. 1.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☒ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

Form PCT/ISA /210 (continuation of first sheet (2)) (July 2009)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CN2013/071091

A. CLASSIFICATION OF SUBJECT MATTER

See the extra sheet
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC: C07D 493/-; C07F 9/-; B01J 31/-; C07B 53/-; C07C 229/-; C07C 227/-

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

REGISTRY, CAPLUS, EPODOC, DWPI, VEN, CNABS, CNKI, CNTXT, EPTXT, USTXT, WOTXT, CATXT, JPTXT: Substructure search according to formula I and II, bidentate, phosphor+, +spiro+, ketal, cataly+, asymmetric, benzopyrano, Ding Kuiling

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CN 102424682 A (SHANGHAI ORGANIC CHEM INST) 25 April 2012 (25.04.2012) see description, pages 3 and 4, examples 1 to 28 and claims 4 to 20	1-3, 11-22
Y		2-12
X	WANG, Xiaoming et al, Catalytic Asymmetric Synthesis of Aromatic Spiroketals by SpinPhox/Iridium(I)-Catalyzed Hydrogenation and Spiroketalization of α,α'-Bis(2-hydroxyarylidene) Ketones, Angewandte Chemie, International Edition, available on web: 14 December 2011, 2012, vol. 51, no. 4, pages 936 to 940, ISSN: 1433-7851, see tables 1 and 2, schemes 1 and 2	1-3, 11-22
Y		2-12

☒ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&"document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
16 April 2013 (16.04.2013)	02 May 2013 (02.05.2013)
Name and mailing address of the ISA State Intellectual Property Office of the P. R. China No. 6, Xitucheng Road, Jimenqiao Haidian District, Beijing 100088, China Facsimile No. (86-10) 62019451	Authorized officer ZHAO, Zhenzhen Telephone No. (86-10) 62086358

Form PCT/ISA /210 (second sheet) (July 2009)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CN2013/071091

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	GIANCARLO, Francio et al, Highly efficient enantioselective catalysis in supercritical carbondioxide using the perfluoroalkyl-substituted ligand(R,S)-3-H2F6-BINAPHOS, Journal of Organometallic Chemistry, 2001, vol. 621, pages 130 to 142, see pages 132, scheme 2	2, 4-5, 11-12
Y	KATRITZKY, Alan R. et al, Comprehensive Organic Functional Group Transformations, no. 2, 2003, pages 826 to 827, see the whole document	6-12
Y	DMITRI, Gelman et al, Copper-Catalyzed C-P Bond Construction via Direct Coupling of Secondary Phosphines and Phosphites with Aryl and Vinyl Halides, Organic Letters, 2003, vol. 5, no. 13, pages 2315 to 2318, see pages 2315 to 2316, table 1	2, 11-12
A	XIN, Yong et al, BF3-promoted cyclization reaction of imines and salicylaldehyde with silyl enol ethers: unexpected formation of dioxaspiro compounds, Tetrahedron, 2008, vol. 64, no. 39, pages 9315 to 9319, ISSN: 0040-4020, see the whole document	1-22
P, A	CN 102746338 A (SHANGHAI ORGANIC CHEM INST), 24 October 2012 (24.10.2012), see the whole document	1-22

Form PCT/ISA /210 (continuation of second sheet) (July 2009)

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/CN2013/071091

Patent Documents referred in the Report	Publication Date	Patent Family	Publication Date
CN 102424682 A	25.04.2012	None	
CN 102746338 A	24.10.2012	None	

Form PCT/ISA /210 (patent family annex) (July 2009)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CN2013/071091

CLASSIFICATION OF SUBJECT MATTER:

C07D 493/10 (2006.01) i

C07D 493/20 (2006.01) i

C07F 9/6561 (2006.01) i

B01J 31/22 (2006.01) i

C07B 53/00 (2006.01) i

C07C 229/34 (2006.01) i

C07C 227/32 (2006.01) i

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REFERENCES CITED IN THE DESCRIPTION

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Non-patent literature cited in the description

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- *Acc. Chem. Res.,* 2008, vol. 41, 581 **[0002]**
- *Chem. Asian J.,* 2009, vol. 4, 32 **[0002]**
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- *Tetrahedron Lett.,* 1998, vol. 39, 5429 **[0003]**
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- *Tetrahedron,* 2006, vol. 62, 5883 **[0003]**
- *Synthesis,* 2008, vol. 22, 3605 **[0003]**
- *Angew. Chem. Int. Ed.,* 2001, vol. 40, 4709 **[0003]**
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- *Angew. Chem. Int. Ed.,* 2001, vol. 40, 4713 **[0003]**
- *Angew. Chem. Int. Ed.,* 2007, vol. 46, 7458 **[0003]**
- *J. Org. Chem.,* 1997, vol. 62, 1058 **[0003]**
- *Org. Lett.,* 2006, vol. 8, 2365 **[0003]**
- *Tetrahedron Lett.,* 2006, vol. 47, 3349 **[0003]**
- *Angew. Chem. Int. Ed.,* 2009, vol. 48, 5345 **[0121]**